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PATENT ABSTRACTS OF JAPAN

(11)Publication number : 2001-213858

(43)Date of publication of application : 07.08.2001

(51)Int.Cl. C07C271/12 A61K 31/17 A61K 31/192

(21)Application number : 2000-355117

(22)Date of filing : 22.11.2000

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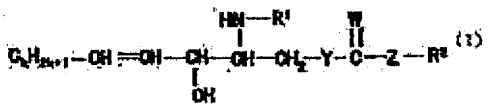
(30)Priority

Priority number : 11332165 Priority date : 24.11.1999 Priority country : JP

(54) DERIVATIVE OF SPHINGOSINE



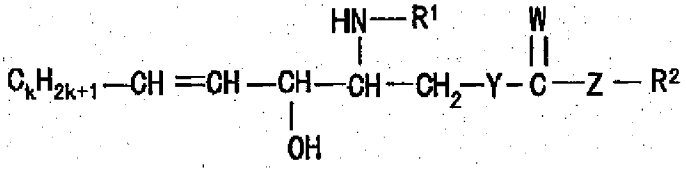
(57)Abstract:

PROBLEM TO BE SOLVED: To provide a new compound having a sphingomyelinase antagonism.

SOLUTION: This compound is a derivative of sphingosine or its pharmaceutically permissible salt expressed by general formula I [R1 is H, a 2-20C alkanoyl, benzoyl or the like, R2 is H, a 1-8C alkyl, -(CH2)nR5 (R5 is hydroxyl, an amino, a pyridyl, a pyrazyl, a morpholinyl, a thiazolyl, a tetrazolyl or the like, n is an integer of 0-5) or SOmR6 (R6 is phenyl or a substituted phenyl substituted with a halogen, a 1-5C alkyl, hydroxyl, an amino, an ureide group or the like, m is 0, 1 or 2.), Z is NR7 (R7 is H, hydroxyl or a 1-5C alkyl), Y is oxygen or NR8 (R8 is H or hydroxyl or a 1-5C alkyl), W is oxygen or sulfur, k is an integer of 1-20].

CLAIMS

[Claim(s)]
[Claim 1]General formula (I)
[Formula 1]



R^1 among [type A hydrogen atom, C_{2-20} alkanoyl group, "Benzoyl, a halogen atom, C_{1-5} alkyl group, a hydroxyl group, C_{1-5} alkoxy group, C_{2-5} alkanoyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, an amino group, The amino group replaced by 1 of C_{1-5} alkyl group, or two pieces, C_{2-5} alkanoyl amino group, C_{2-5} alkoxycarbonylamino group, C_{1-5} alkyl group replaced by 1-5 of the halogen atom, The benzoyl replaced by the cyano group, the nitro group, the sulfhydryl group, or C_{1-5} alkylthio group", C_{4-8} cycloalkyl carbonyl group, C_{2-20} alkoxycarbonyl group, Formula-$COC(R^3)_2NHR^4$ (among a formula, R^3 is a hydrogen atom or C_{1-5} alkyl group, and) R^4 is a hydrogen atom or C_{2-5} alkoxycarbonyl group. It is a basis shown by basis or formula-$COCO_2R^3$ (R^3 is a hydrogen atom or C_{1-5} alkyl group among a formula.) shown, R^2 is hydrogen atom, C_{1-8} alkyl group, and formula-$(CH_2)_nR^5$ (among a formula). The amino group by which R^5 was replaced by 1-3 pieces, a hydroxyl group, an amino group, and C_{1-5} alkyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, a carbamoyl group, The aminocarbonyl group replaced by 1 of C_{1-5} alkyl group, or two pieces, The aminocarbonyl oxy group replaced by 1 of a carbamoyloxy group and C_{1-5} alkyl group, or two pieces, "A phenyl group, a halogen atom, C_{1-5} alkyl group, a hydroxyl group, C_{1-5} alkoxy group, C_{2-5} alkanoyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, an amino group, The amino group replaced by 1 of C_{1-5} alkyl group, or two pieces, The ureido group replaced by 1 of C_{2-5} alkanoyl amino group, C_{2-5} alkoxycarbonylamino group, C_{1-5} alkyl group replaced by 1-5 of the halogen atom, a cyano group, a nitro group, an ureido group, and C_{1-5} alkyl group, or two pieces, The phenyl group replaced by the sulfhydryl group or C_{1-5} alkylthio group", A pyridyl group, the pyridyl group replaced by C_{1-5} alkoxy group, A pyrazyl group, a pyrrolidyl group, a piperidyl group, a PIPERAJIRU group, a morpholinyl group, A thiomorpholinyl group, an imidazolyl group, a thiazolyl group, a thiadiazolyl group, it is a tetrazolyl group, a quinolyl group, or a 1H-indazolyl group, and n is an integer of 0-5 -- basis [which is shown] or formula-SO_mR^6 (among a formula) R^6 A phenyl group or "halogen atom, C_{1-5} alkyl group, A hydroxyl group, C_{1-5} alkoxy group, C_{2-5} alkanoyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, an amino group, The amino group replaced by 1 of C_{1-5} alkyl group, or two pieces, The ureido group replaced by 1 of C_{2-5} alkanoyl amino group, C_{2-5} alkoxycarbonylamino group, C_{1-5} alkyl group replaced by 1-5 of the halogen atom, a cyano group, a nitro group, an ureido group, and C_{1-5} alkyl group, or two pieces, it is the phenyl group replaced by the sulfhydryl group or C_{1-5} alkylthio group", and m is 0, 1, or 2 -- it is a basis shown -- Z -- NR^7 (here) R^7 is a hydrogen atom, a hydroxyl group, or C_{1-5}

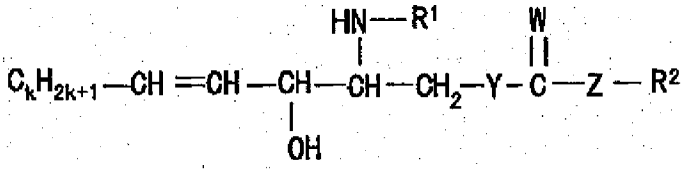
alkyl group. It is, Y is an oxygen atom or NR^8 (R^8 is a hydrogen atom, a hydroxyl group, or C_{1-5} alkyl group.), W is an oxygen atom or a sulfur atom, and k is an integer of 1-20. The sphingosine derivative expressed with], or its salt permitted pharmacologically.
[Claim 2]The sphingosine derivative according to claim 1 whose Y R^1 is an isobutyryl group or a pivaloyl group, and is an oxygen atom in general formula (I), whose Z is NH and whose k is 13, or its salt permitted pharmacologically.
[Claim 3]The sphingosine derivative according to claim 1 whose R^1 is an isobutyryl group or a pivaloyl group, Y and whose Z are NH(s) in general formula (I) and whose k is 13, or its salt permitted pharmacologically.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]Neutral sphingomyelinase is checked in this invention.
Therefore, it is related with a new sphingosine derivative useful as various medicines.

[0002]
[Description of the Prior Art]By using as a substrate sphingomyelin which is one of the sphingolipid which mainly exists in a cell membrane, sphingomyelinase is an enzyme disassembled into ceramide and the phosphocholine, and is divided roughly into an acid type and a neutral type from the optimal pH of the activity manifestation. Although a neutral type exists in a cell membrane or cytoplasm to an acid type carrying out localization to lysosome, both types are considered to participate in generation of the ceramide by the metabolic turnover of sphingomyelin.
[0003]The ceramide generated by sphingomyelinase has played the important role in various cell functions, such as apoptosis, cell growth, and differentiation, as a lipid second messenger, and this metabolic turnover production course is called the sphingomyelin course.
[0004]Sphingomyelinase The ischemia, TNF-alpha, IL-1beta, IFN-gamma, Since various stress, such as 1 alpha, 25-dihydroxy vitamin D_3, an anticancer agent, or radiation, is activated, it is possible that the sphingomyelin course is participating in the various symptoms chemical [these] and whose physical stress caused its onset and progress. For example, although a sphingomyelin course is activated at the time of brain ischemia, the sphingomyelinase to a brain-cell or addition of ceramide causes the cell death by apoptosis. Although production of TNF-alpha or IL-1beta rises at the time of brain ischemia and neuron death is induced, the solubilization receptor of TNF-alpha and the receptor antagonism agent of IL-1beta control the neuron death by the ischemia.

[0005]Production sthenia of TNF-alpha or IL-1beta is participating in cranial nerve degenerative diseases, such as head injury, senile dementia, an Alzheimer disease, and a Parkinson Mr. disease, widely besides the above-mentioned cerebrovascular disease.
[0006]Although production of TNF-alpha in fat cells rises and insulin resistance is derived in non-insulin dependent diabetes mellitus and obesity, activation of the sphingomyelin course by TNF-alpha is participating in this. Although IL-1beta participates in the onset of insulin dependent diabetes mellitus, ceramide reveals the same operation as IL-1beta.
[0007]TNF-alpha and IL-1beta participates also in the process of the onset and progress of arteriosclerosis. That is, TNF-alpha and IL-1beta makes ICAM-1 of an adhesion factor reveal in a vascular endothelial cell, and promotes adhesion to a monocytic vascular endothelial cell, and the migration to the bottom of an inner bark. TNF-alpha causes the apoptosis of a vascular endothelial cell via activation of a sphingomyelin course. Activation of a sphingomyelin course promotes the LDL condensation by a vascular smooth muscle, and forms a lesion, and it destabilizes a plaque via the apoptosis of a vascular smooth muscle.
[0008]The physiology activity of the ceramide in an inflammation immune system cell is dramatically variegated, and is participating in the onset and progress of various inflammatory diseases and an immune disease deeply via derivation of differentiation and activation of a T cell and a B cell, various cytokine production, and apoptosis, production of an inflammatory prostagladin, etc. Since very much chemical and physical stress including TNF-alpha or IL-1beta participate in activation of a sphingomyelin course, it is thought that many cell lineage and signaling pathways are carrying out the cross talk to these symptoms intricately mutually.
[0009]From the above thing, specific inhibitor to sphingomyelinase, It can be used as the preventive medicine to cranial nerve degenerative diseases, such as cerebrovascular disease, such as cerebral hemorrhage and cerebral infarction, head injury, senile dementia, an Alzheimer disease, and a Parkinson Mr. disease, diabetes mellitus, obesity, arteriosclerosis, an inflammatory disease, an immune disease, cancer, a renal disease, and a heart disease, and a remedy.
[0010]As a sphingosine derivative which has sphingomyelinase inhibitory action. Although 3-O-alkyl sphingomyelin is reported (Mark D.Lister, et al., Biochimica et Biophysica Acta, 1995, 1256, 25), the compound and chemical structure of this invention differ from each other.
[0011]
[Problem(s) to be Solved by the Invention]An object of this invention is to provide the new compound which has sphingomyelinase inhibitory action.
[0012]
[Means for Solving the Problem]In order to attain said technical problem, as a result of advancing research wholeheartedly, this invention persons found out that a certain kind of sphingosine derivative had neutral sphingomyelinase inhibiting activity, and completed this invention. That is, this invention is general formula (I).
[0013]
[Formula 2]



R^1 among [type A hydrogen atom, C_{2-20} alkanoyl group, "Benzoyl, a halogen atom, C_{1-5} alkyl group, a hydroxyl group, C_{1-5} alkoxy group, C_{2-5} alkanoyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, an amino group, An amino group replaced by 1 of C_{1-5} alkyl group, or two pieces, C_{2-5} alkanoyl amino group, C_{2-5} alkoxycarbonylamino group, C_{1-5} alkyl group replaced by 1-5 of a halogen atom, Benzoyl replaced by cyano group, nitro group, sulfhydryl group, or C_{1-5} alkylthio group", C_{4-8} cycloalkyl carbonyl group, C_{2-20} alkoxycarbonyl group, Formula-$COC(R^3)_2NHR^4$ (among a formula, R^3 is a hydrogen atom or C_{1-5} alkyl group, and) R^4 is a hydrogen atom or C_{2-5} alkoxycarbonyl group. It is a basis shown by basis or formula-$COCO_2R^3$ (R^3 is a hydrogen atom or C_{1-5} alkyl group among a formula.) shown, R^2 is hydrogen atom, C_{1-8} alkyl group, and formula-$(CH_2)_nR^5$ (among a formula). An amino group by which R^5 was replaced by 1-3 pieces, a hydroxyl group, an amino group, and C_{1-5} alkyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, a carbamoyl group, An aminocarbonyl group replaced by 1 of C_{1-5} alkyl group, or two pieces, An aminocarbonyl oxy group replaced by 1 of a carbamoyloxy group and C_{1-5} alkyl group, or two pieces, "A phenyl group, a halogen atom, C_{1-5} alkyl group, a hydroxyl group, C_{1-5} alkoxy group, C_{2-5} alkanoyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, an amino group, An amino group replaced by 1 of C_{1-5} alkyl group, or two pieces, An ureido group replaced by 1 of C_{2-5} alkanoyl amino group, C_{2-5} alkoxycarbonylamino group, C_{1-5} alkyl group replaced by 1-5 of a halogen atom, a cyano group, a nitro group, an ureido group, and C_{1-5} alkyl group, or two pieces, A phenyl group replaced by sulfhydryl group or C_{1-5} alkylthio group", A pyridyl group, a pyridyl group replaced by C_{1-5} alkoxy group, A pyrazyl group, a pyrrolidyl group, a piperidyl group, a PIPERAJIRU group, a morpholinyl group, A thiomorpholinyl group, an imidazolyl group, a thiazolyl group, a thiadiazolyl group, it is a tetrazolyl group, a quinolyl group, or a 1H-indazolyl group, and n is an integer of 0-5 -- basis [which is shown] or formula-SO_mR^6 (among a formula) R^6 A phenyl group or "halogen atom, C_{1-5} alkyl group, A hydroxyl group, C_{1-5} alkoxy group, C_{2-5} alkanoyl group, A carboxyl group, C_{2-5} alkoxycarbonyl group, an amino group, An amino group replaced by 1 of C_{1-5} alkyl group, or two pieces, An ureido group replaced by 1 of C_{2-5} alkanoyl amino group, C_{2-5} alkoxycarbonylamino group, C_{1-5} alkyl group replaced by 1-5 of a halogen atom, a cyano group, a nitro group, an ureido group, and C_{1-5} alkyl group, or two pieces, it is the phenyl group replaced by sulfhydryl group or C_{1-5} alkylthio group", and m is 0, 1, or 2 -- it is a basis shown -- Z -- NR^7 (here) R^7 is a hydrogen atom, a hydroxyl group, or C_{1-5} alkyl group. It is, Y is an oxygen atom or NR^8 (R^8 is a hydrogen atom, a hydroxyl group, or C_{1-5} alkyl group.), W is an oxygen atom or a sulfur atom, and k is an integer of 1-20. They are a sphingosine derivative expressed with], or its salt permitted pharmacologically.

[0014]C_{2-20} alkanoyl group as used in this invention means a straight chain or a branched-chain

alkanoyl group with 2-20 carbon atoms, For example, an acetyl group, a propanoly group, isopropano yl groups, a butyryl group, an isobutyryl group, a valeryl group, a pivaloyl group, a milli styryl group, a stearyl group, etc. can be mentioned.
[0015]The number of carbon atoms means a thing of 2-5 among the above [C_{2-5} alkanoyl group].
[0016]C_{4-8} cycloalkyl carbonyl group means a cycloalkyl carbonyl group with 4-8 carbon atoms, for example, a cyclo propylcarbonyl group, a cyclopentyl carbonyl group, a cyclohexyl carbonyl group, a cycloheptyl carbonyl group, etc. can be mentioned.
[0017]C_{2-5} alkoxycarbonyl group means a straight chain or a branched-chain alkoxycarbonyl group with 2-5 carbon atoms, For example, a methoxycarbonyl group, an ethoxycarbonyl group, an ethoxycarbonyl group, a carbopropoxy group, a tert-butoxycarbonyl group, etc. can be mentioned.
[0018]C_{1-20} alkyl group means a straight chain or a branched-chain alkyl group with 1-20 carbon atoms, For example, a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, An isobutyl group, a tert-butyl group, a pentyl group, an isopentyl group, a hexyl group, an isohexyl group, a heptyl group, an octyl group, a nonyl group, a decyl group, a tridecyl group, a nonadecyl group, etc. can be mentioned.
[0019]C_{1-8} alkyl group means a thing with 1-8 carbon atoms among the above, and C_{1-5} alkyl group means a thing with 1-5 carbon atoms among the above.
[0020]An amino group replaced by 1-3 of C_{1-5} alkyl group means that a nitrogen atom of an amino group is replaced by C_{1-5} alkyl group, and means that it is the 4th class salt that three pieces are replaced.
[0021]C_{2-5} alkanoyl amino group means that a nitrogen atom of an amino group is replaced by one of C_{2-5} alkanoyl group, for example, an acetylamino group, an isopropionylamino group, etc. can be mentioned.
[0022]C_{2-5} alkoxycarbonylamino group means that a nitrogen atom of an amino group is replaced by one of C_{2-5} alkoxycarbonyl group, for example, a methoxycarbonylamino group, a butoxycarbonylamino group, etc. can be mentioned.
[0023]A halogen atom is a fluorine atom, a chlorine atom, a bromine atom, or iodine atoms. C_{1-5} alkyl group replaced by 1-5 of a halogen atom means a straight chain or a branched-chain alkyl group with 1-5 carbon atoms replaced with said halogen atom, for example, a trifluoromethyl group etc. can be mentioned.
[0024]C_{1-5} alkoxy group means a straight chain or a branched-chain alkoxy group with 1-5 carbon atoms, for example, a methoxy group, an ethoxy basis, a propoxy group, an isopropoxy group, a butoxy group, a heptoxy group, etc. can be mentioned.
[0025]C_{1-5} alkylthio group means a straight chain or a branched-chain alkylthio group with 1-5 carbon atoms, For example, a methylthio group, an ethyl thio group, a propyl thio group, an isopropyl thio group, a butyl thio group, an isobutyl thio group, a tert-butyl thio group, a pentyl thio group, a hexyl thio group, etc. can be mentioned.
[0026]As a protective group of a hydroxyl group, acetal type protective groups, such as 3

substitution silyl group; tetrahydropyranyloxy groups, such as acyl group; trimethylsilyl groups, such as an acetyl group and benzoyl, t-butyldimethylsilyl group, and a benzyl dimethylsilyl group, and a methoxymethyl group, etc. can be mentioned.

[0027]When a substituent expressed with two or more same signs in one general formula exists, they may be the same or may differ.

[0028]Salts permitted pharmacologically show acid or alkali addition salt. In this case, although there is no restriction in particular in acid or alkali to be used, as acid, chloride, sulfuric acid, nitric acid, acetic acid, benzenesulfonic acid, etc. can be mentioned, and ammonium ion, such as metal ions, such as sodium and potassium, and alkylammonium, etc. can be mentioned as alkali.

[0029]A compound of this invention may be a single optically active substance, or may be a mixture of a stereoisomeric form.

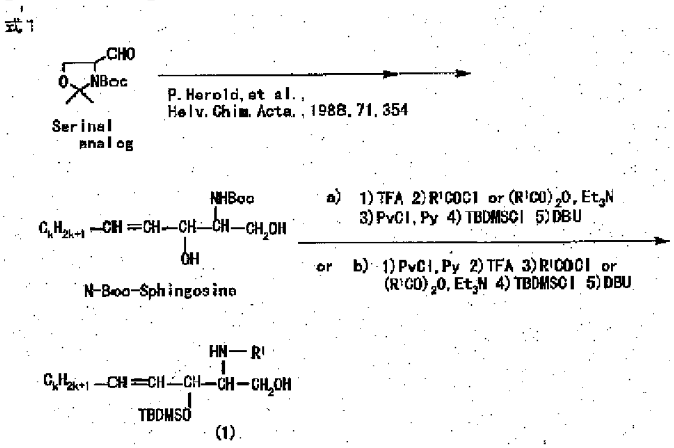
[0030]A compound of this invention can be manufactured in accordance with a method shown below, for example.

[0031]In this specification, Boc hereafter A tert-butoxycarbonyl group, As for TFA, a pivaloyl group and DBU trifluoroacetic acid and Pv 1,8-diazabicyclo[5.4.0]undec-7-ene, As for TCF, chloroformic acid trichloromethyl and TBDMS express a tert-butyldimethylsilyl group, WSC-HCl expresses a 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, and HOBt may express 1-hydroxybenzotriazol, respectively.

[0032]First, N-Boc-sphingosine which is synthetic powder can be compounded from serinal in accordance with a method (Helv.Chim.Acta., 1988, 71,354) of P.Herold and others, and can compound an intermediate compound (1) by a method subsequently to the formula 1 shown.

[0033]

[Formula 3]



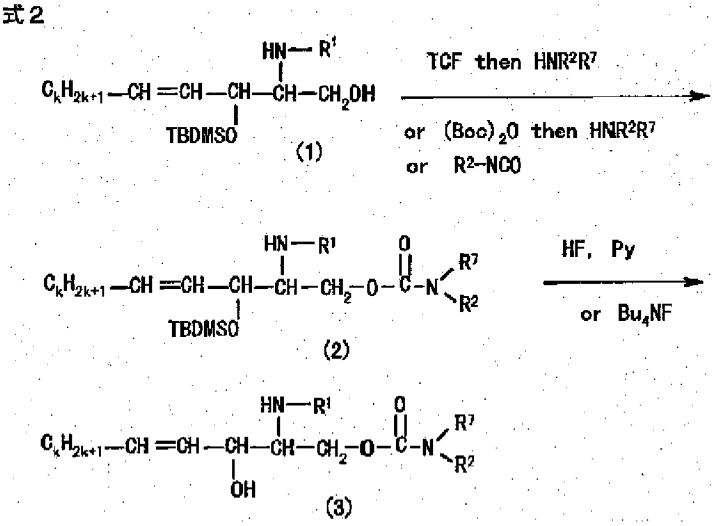
In the compound of general formula (I), the compound (3) Y and whose W are oxygen atoms and whose Z is NR^7 can be manufactured by the method shown in the formula 2. That is, after processing a compound (1) for bottom chloroformic acid trichloromethyl of base existence, or 2 di-tert-butyl carbonate, a compound (2) can be obtained by making it react to a corresponding amine compound. A compound (2) can also be obtained by making an intermediate (1) react to a corresponding isocyanate. A compound (3) can be obtained by desilanizing a compound (2) with

hydrofluoric acid or tetrabutylammonium fluoride. Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0034]

[Formula 4]

式 2

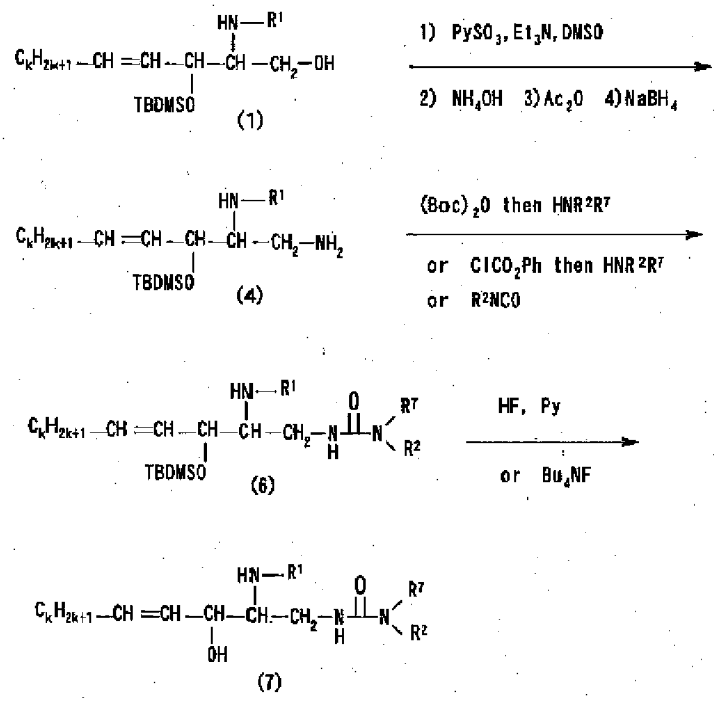


In the compound of general formula (I), the compound (7) whose Y is NH, whose W is an oxygen atom and whose Z is NR^7 can be manufactured by the method shown in the formula 4. Namely, after oxidizing by a sulfur trioxide pyridine complex and triethylamine and using a compound (1) as an aldehyde object among dimethyl sulfoxide, It was made to react to hydroxylamine and an acetic anhydride one by one, the generated acetoxyimine object was returned with sodium borohydride, and it changed into the amine compound (4). Although the example using TBDMS as a protective group of a hydroxyl group is shown in the formula 3, other amine compounds can be manufactured using other above-mentioned protective groups or by carrying out deprotection on condition of common use. Subsequently, after processing a compound (4) for chloroformic acid phenyl or 2 di-tert-butyl carbonate, a compound (6) can be obtained by making it react to a corresponding amine compound. A compound (6) can also be obtained by making a compound (4) react to a corresponding isocyanate. A compound (7) can be obtained by desilanizing a compound (6). Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0035]

[Formula 5]

式4

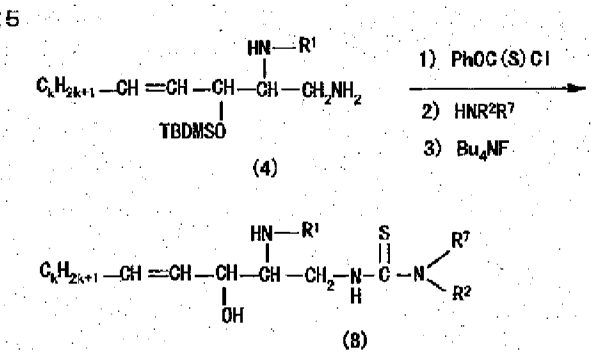


In the compound of general formula (I), the compound (8) whose Y is NH, whose W is a sulfur atom and whose Z is NR^7 can be manufactured by the method shown in the formula 5. That is, a compound (8) can be obtained by making a compound (4) react to the isothiocyanate which makes it react to chloro CHIONO formic acid phenyl and an amine compound corresponding after a reaction, or corresponds, and desilanizing it further. Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0036]

[Formula 6]

式5

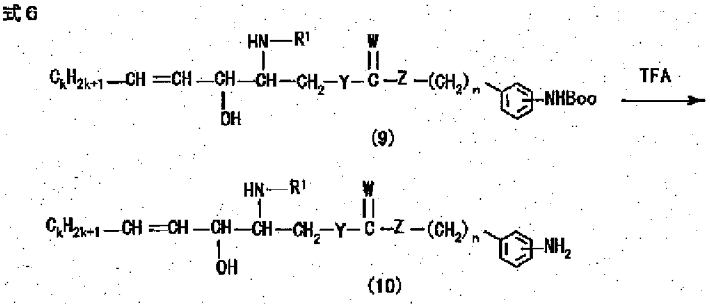


In the compound of general formula (I), the compound (10) and compound (11) whose R^2 is a basis shown by formula-$(CH_2)_nR^5$ (phenyl group by which R^5 was replaced with the amino group or C_{2-5} alkanoyl amino group), It can manufacture by the method shown in the formula 6. That is, trifluoroacetic acid removes Boc for the compound (9) obtained by one which is shown

by said formulas 2-5 of methods, and a compound (10) is obtained. When considering it as an acetylamino group, it can change into a compound (11) by making it react to an acetic anhydride further. Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0037]

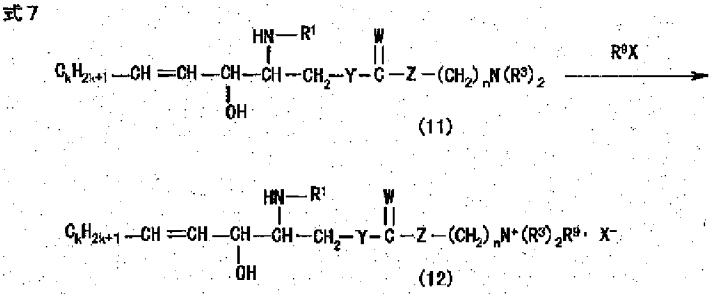
[Formula 7]



In the compound of general formula (I), R^2 can manufacture the compound (13) which is a basis shown by formula-$(CH_2)_nR^5$ (R^5 is the 4th class amine) by the method shown in the formula 7. That is, a compound (13) can be obtained by making the compound (12) obtained by one which is shown by said formulas 2-5 of methods react to corresponding alkyl halide. Reaction conditions, such as a reagent in this reaction, time, temperature, and a solvent, can be performed on the conditions usually used.

[0038]

[Formula 8]

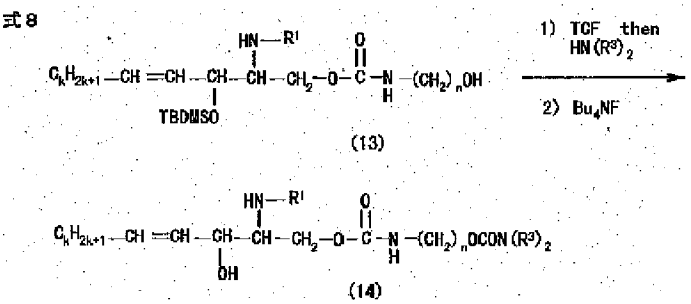


(R^9 shows C_{1-5} alkyl group among a formula, and X shows a halogen atom.) In the compound of general formula (I), The compound (15) whose R^2 is a basis shown by formula-$(CH_2)_nR^5$ (aminocarbonyl oxy group with which R^5 was replaced by 1 of a carbamoyloxy group or C_{1-5} alkyl group, or two pieces), It can manufacture by the method shown by the formula 8. That is, after processing the compound (14) obtained by one which is shown by said formulas 2-5 of methods by chloroformic acid trichloromethyl, a compound (15) can be obtained by making it react to a corresponding amine compound, and desilanizing further. Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0039]

[Formula 9]

式 8



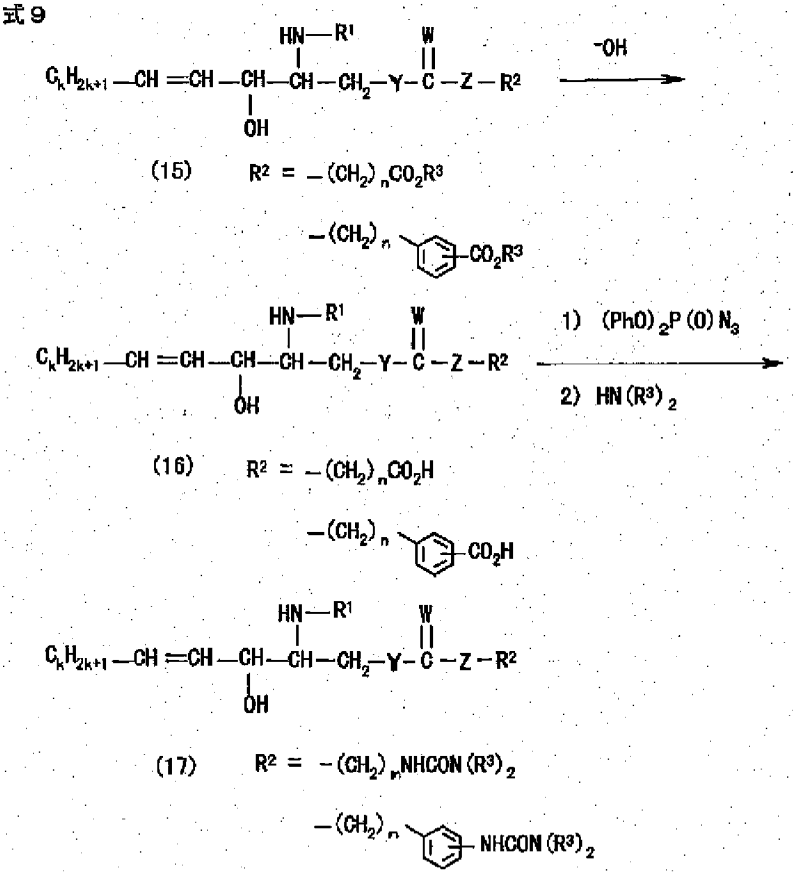
In the compound of general formula (I), the compound (17) whose R^2 is a basis shown by formula-$(CH_2)_nR^5$ (phenyl group by which R^5 was replaced by the carboxyl group or the carboxyl group), As the formula 9 showed, the compound (16) obtained by one which is shown by said formulas 2-5 of methods can be hydrolyzed by the usual method of hydrolyzing ester.

[0040]After processing a compound (17) by diphenylphosphoric acid azide, a compound (18) can be obtained by making it react to a corresponding amine compound. Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0041]

[Formula 10]

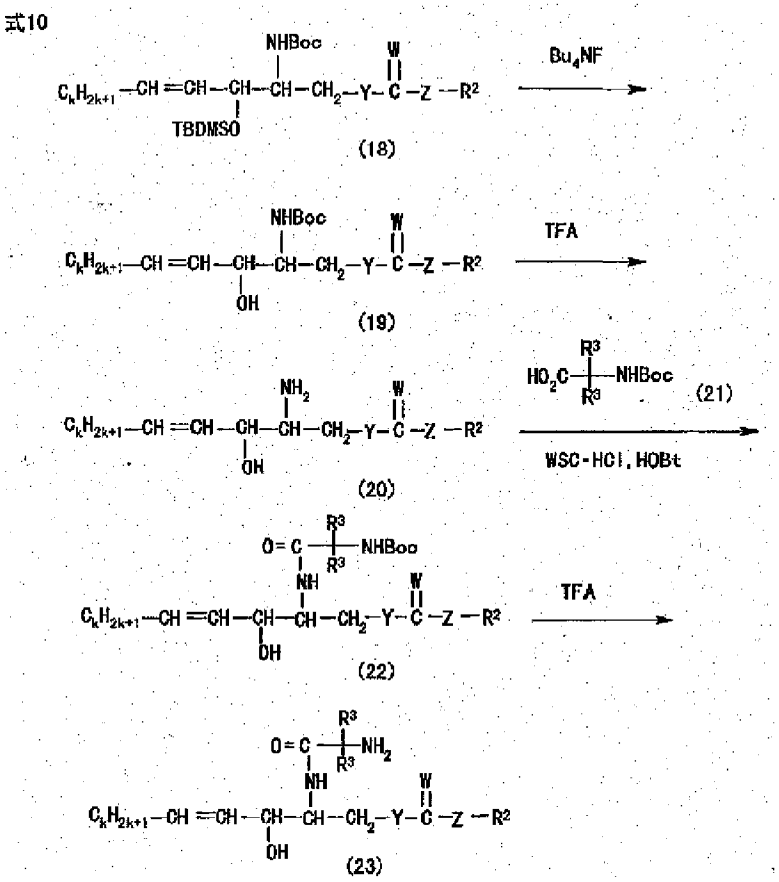
式 9



As shown in the formula 10, a compound (20) can be obtained by desilanizing the compound (19) led from N-Boc-sphingosine. Subsequently, the compound (20) obtained here can be processed with trifluoroacetic acid, and a compound (21) can be obtained. A compound (23) can be obtained by condensing a compound (21) and an amino acid derivative (22). A compound (23) can be processed with trifluoroacetic acid and can be changed into a compound (24). Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0042]

[Formula 11]

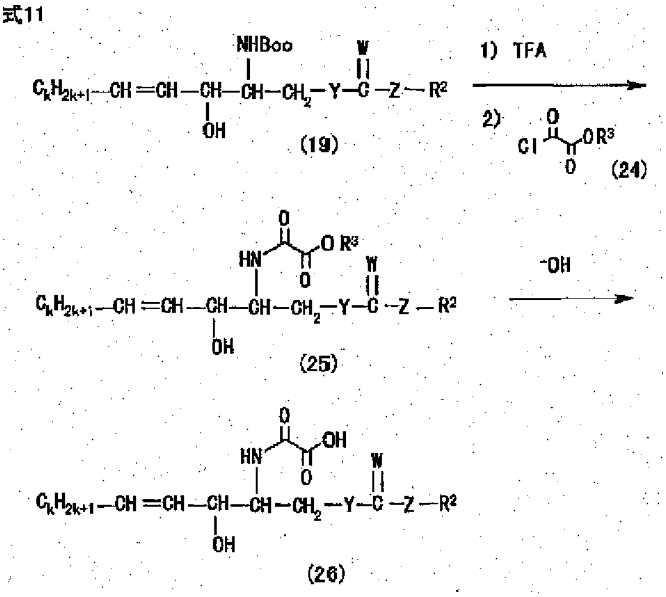


As shown in the formula 11, a compound (25) can be obtained by making a compound (21) react to the halide of a compound (27). It is convertible for a compound (26) by hydrolyzing a compound (25). Reaction conditions, such as a reagent in these reactions, time, temperature, and a solvent, can be performed on the conditions usually used.

[0043]

[Formula 12]

式11



[Effect of the Invention]The new sphingosine derivative of this invention Cerebrovascular disease, such as cerebral hemorrhage and cerebral infarction, It can be used as the preventive medicine to cranial nerve degenerative diseases, such as head injury, senile dementia, an Alzheimer disease, and a Parkinson Mr. disease, diabetes mellitus, obesity, arteriosclerosis, an inflammatory disease, an immune disease, cancer, a renal disease, and a heart disease, and a remedy.

[0044]

[Example]Hereafter, a reference example, an example, and the example of an examination are given, and this invention is explained still in detail.

[0045]2-N-(tert-butoxycarbonyl)-D-erythro sphingosine was manufactured according to the method given in literature (P. Herold, et al., Helv.Chim.Acta., 1988, 71,354).

[0046]The ^{1}H-NMR-spectrum value described below was measured at 200 MHz (when there is no statement in particular).

At the dichloromethane (60 ml) solution of reference example 12-N-(tert-butoxycarbonyl)-D-erythro sphingosine (5.6 g,14mmol), the bottom trifluoroacetic acid (12 ml) of -20 ** cooling was dropped, and temperature up was carried out to the room temperature over 3 hours to it. The solvent was distilled off, and to the residue, hydrous methanol (water: methanol =12ml:200ml) and after adding potassium carbonate (3.8g) subsequently, it stirred at the room temperature for 24 hours. Column chromatography refined the residue after distilling off a solvent, and D-erythro sphingosine (5.5g) was obtained.

[0047]The compound obtained here was dissolved in the tetrahydrofuran (60 ml), the bottom triethylamine of ice-cooling (5.1 ml, 37mmol) was added, and, subsequently pivaloyl chloride (1.8 ml, 15mmol) was dropped. After stirring under the temperature for 1 hour, saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. After desiccation and a solvent were distilled off for the extract with magnesium sulfate, column chromatography

refined the residue, and 2-N-pivaloyl D-erythro sphingosine (3.4g) was obtained.
^{1}H-NMR. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.4Hz,3H),1.08-1.47(m,22H),1.21(s,9H),1.95-2.13(m,2H),2.83-3.07(m,2H),3.69(m,1H),3.78-4.02(m, 2H, 4.29(m,1H),5.51(dd,J=6.5,15.4Hz,1H),5.77(dt,J=15.4,6.9Hz,1H),6.42(d,J=6.8Hz,1H) [0048]The compound (0.90 g, 2.3mmol) obtained by the reference example 2 reference example 1 was melted in pyridine (8 ml), pivaloyl chloride (0.35 ml) was dropped under -10 ** cooling, and it stirred under the temperature for 3 hours. After adding water to reaction mixture, ethyl acetate extracted and it dried with magnesium sulfate. The solvent was distilled off, column chromatography refined the residue and 2-N and 1-O-dipivaloyl D-erythro sphingosine (0.90g) were obtained.
^{1}H-NMR. ($CDCl_3$) delta(ppm):0.88(t,J=6.9Hz,3H),1.19(s,9H),1.20(s,9H),1.23-1.42(m,22H),1.99-2.10(m,2H),3.09(bs,1H),4.14(dd,J=3.9, 11.4Hz,1H),4.17(m,1H),4.24(m,1H),4.34(dd,J=7.0,11.4Hz,1H),5.46(ddt,J=6.6,15.4,1.3Hz,1H),5.75(ddt,J=0.9, 15.4, 1.3 Hz, 1H, 6.09(d,J=7.6Hz,1H)[0049]The compound (2.3 g, 5.0mmol) obtained by the reference example 3 reference example 2 is melted in N.N-dimethylformamide (10 ml), Imidazole (2.72 g, 10mmol) was added, subsequently tert-butyldimethylsilyl chloride (2.7 g, 18mmol) was added, and it stirred at 60 ** for 17 hours. After condensing reaction mixture by decompression, column chromatography refined the residue and 3-O-(tert-butyldimethylsilyl)-2-N and 1-O-dipivaloyl D-erythro sphingosine (2.8g) were obtained.
^{1}H-NMR. ($CDCl_3$) delta(ppm) : 0.01(s,3H),0.04(s,3H),0.88(t,J=6.7Hz,3H),0.88(s,9H),1.15(s,9H),1.16(s,9H),1.22-1.38(m,22H),1.93-2.04(m, 2H),3.29(dd,J=4.6,9.0Hz,1H),3.63(dd,J=3.6,9.0Hz,1H),3.91(m,1H),4.17(dd,J=6.7,7.4Hz,1H),5.42(dd,J=7.4,15.4Hz, 1H, 5.57(dt,J=15.4,6.7Hz,1H),5.91(d,J=8.6Hz,1H) [0050]The output (2.8 g, 4.8mmol) acquired by the reference example 4 reference example 3 was melted in non-aqueous methanol (30 ml), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.68 g, 4.5mmol) was added, and it stirred for three days at the room temperature. Reaction mixture was condensed by decompression, column chromatography refined the residue, and 3-O-(tert-butyldimethylsilyl)-2-N-pivaloyl D-erythro sphingosine (2.2g) was obtained.
^{1}H-NMR. ($CDCl_3$) delta(ppm):0.03(s,3H),0.06(s,3H),0.87(t,J=6.5Hz,3H),0.90(s,9H),1.02-1.44(m,22H),1.15(s,9H),1.93-2.11(m,2H),3.42(d, J=9.8Hz,1H),3.56(ddd,J=3.0,9.8,11.0Hz,1H),3.76(m,1H),4.00(dd,J=2.3,11.0Hz,1H),4.42(m,1H), 5.44(dd,J=6.3-15.4Hz, 1H, 5.76(dt,J=15.4,6.6Hz,1H),6.52(d,J=7.0Hz,1H) [0051]Reference example 52-N-(tert-butoxycarbonyl)-D-erythro sphingosine (2.0 g, 5.0mmol) was melted in pyridine (20 ml), and pivaloyl chloride (0.66 g, 5.5mmol) was dropped under -20 ** cooling. After returning reaction mixture to a room temperature over 2 hours, saturated sodium bicarbonate water was added and ethyl acetate extracted. The solvent was distilled off for the extract after desiccation with magnesium sulfate, column chromatography refined the residue, and 2-N-(tert-butoxycarbonyl)-1-O-pivaloyl D-erythro sphingosine (2.2g) was obtained.
^{1}H-NMR. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.9Hz,3H),1.21(s,9H),1.21-

1.41(m,22H),1.44(s,9H),2.00-2.08(m,2H),2.33(bs,1H),3.94(m,1H),4.12(dd, J=4.4,11.4Hz,1H),4.15(m,1H),4.26(dd,J=6.6,11.4Hz,1H),4.80(bd,J=7.8Hz,1H),5.49(dd,J=6.8,15.4Hz,1H),5.75 (dt, J= 15.4, 6.8 Hz, 1H) [0052]The compound (2.2 g, 4.5mmol) obtained by the reference example 5 was added to reference example 6 trifluoroacetic acid (14 ml) under ice-cooling, and temperature up was carried out to the room temperature over 3 hours. After condensing reaction mixture by decompression, ethanol was added and it condensed again. The residue was melted in the tetrahydrofuran (14 ml), the bottom triethylamine of ice-cooling (1.4 g, 14mmol) was added, subsequently the isobutyric anhydride (0.85 g, 5.4mmol) was added, and it stirred under the temperature for 1.5 hours. Ethyl acetate extracted, after adding water to reaction mixture. It condensed, after drying an extract with sodium sulfate. Melt a residue in N.N-dimethylformamide (14 ml), and imidazole (1.6 g, 24mmol) is added, Subsequently, tert-butyldimethylsilyl chloride (1.2 g, 8.1mmol) was added, and it stirred at the room temperature for 8 hours, and water was added after concentration under decompression and ethyl acetate extracted reaction mixture. The solvent was distilled off after desiccation with sodium sulfate, column chromatography refined the residue, and 3-O-(tert-butyldimethylsilyl)-2-N-isobutyryl 1-O-pivaloyl D-erythro sphingosine (2.3g) was obtained.

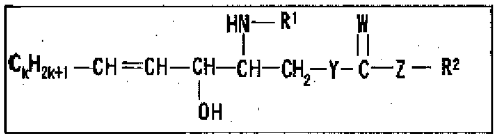
[0053]The compound (2.3 g, 4.0mmol) obtained here was melted in drying methanol (30 ml), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.92 g, 6.4mmol) was added, and it stirred at the room temperature for 28 hours. Reaction mixture was condensed by decompression, column chromatography refined the residue, and 3-O-(tert-butyldimethylsilyl)-2-N-isobutyryl D-erythro sphingosine (1.9g) was obtained.

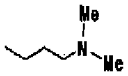
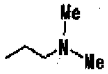
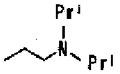
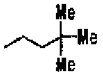
^{1}H-NMR ($CDCl_3$) delta (ppm):0.02 (s, 3H), 0.05 (s, 3H), 0.85 (t, J= 6.7 Hz, 3H), 0.89 (s, 9H), 1.13. (d, J= 6.8 Hz, 6H), 1.08-1.44(m,22H),1.94-2.14(m,2H),2.38(m,1H),3.31(m,1H),3.54(m,1H),3.77(m,1H),4.01(dd,J=3.0,11.3Hz,1H), 4.42(dd,J=2.9,6.0Hz,1H),5.44(dd,J=6.2,15.4Hz,1H),5.71(dt,J=15.4,6.8Hz,1H),6.29(d,J=7.4Hz,1H) [0054]The compound of this invention manufactured in Example 104 from the following Examples 1 was shown in the following tables.

[0055]

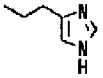
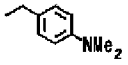
[Table 1]

表1

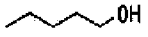
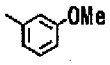
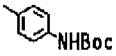
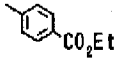
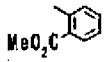
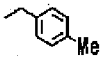
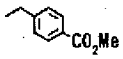


実施例	k	R^1	R^2	Y	Z	W
1	13	tBuCO	H	O	NH	O
2	13	tBuCO	OH	O	NH	O
3	13	tBuCO		O	NH	O
4	13	tBuCO		O	NH	O
5	13	tBuCO		O	NH	O
6	13	tBuCO		O	NH	O
7	13	tBuCO		O	NH	O
8	13	tBuCO		O	NH	O
9	13	tBuCO		O	NH	O
10	13	tBuCO		O	NH	O
11	13	tBuCO		O	NH	O
12	13	tBuCO		O	NH	O
13	13	tBuCO		O	NH	O
14	13	tBuCO		O	NH	O

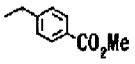
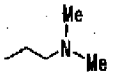
[Table 2]

実施例	k	R^1	R^2	Y	Z	W
15	13	tBuCO		O	NH	O
16	13	tBuCO		O	NH	O
17	13	tBuCO		O	NH	O
18	13	tBuCO		O	NH	O
19	13	PhCO		O	NH	O
20	13	tBuCO		O	NH	O
21	13	tBuCO		O	NH	O
22	13	tBuCO		O	NH	O
23	13	tBuCO		O	NH	O
24	13	tBuCO		O	NH	O
25	13	tBuCO		O	NH	O
26	13	tBuCO		O	NH	O
27	13	tBuCO		O	NH	O
28	13	iPrCO	H	O	NH	O
29	13	iPrCO		O	NH	O
30	13	iPrCO		O	NH	O

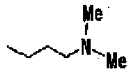
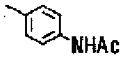
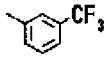
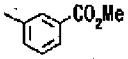
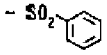
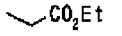
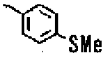
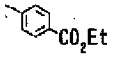
[Table 3]

実施例	k	R^1	R^2	Y	Z	W
31	13	iPrCO		O	NH	O
32	13	iPrCO		O	NH	O
33	13	iPrCO		O	NH	O
34	13	iPrCO		O	NH	O
35	13	iPrCO		O	NH	O
36	13	iPrCO		O	NH	O
37	13	iPrCO		O	NH	O
38	13	iPrCO		O	NH	O
39	13	iPrCO		O	NH	O
40	13	iPrCO		O	NH	O
41	13	iPrCO		O	NH	O
42	13	iPrCO		O	NH	O
43	13	iPrCO		O	NH	O
44	13	iPrCO		O	NH	O
45	13	iPrCO		O	NH	O
46	13	iPrCO		O	NH	O

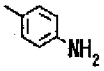
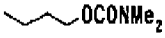
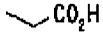
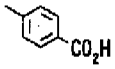
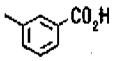
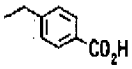
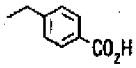
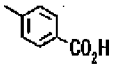
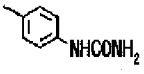
[Table 4]

実施例	k	R^1	R^2	Y	Z	W
47	13	iPrCO		O	NH	O
48	13	iPrCO		O	NH	O
49	13	iPrCO		O	NH	O
50	13	iPrCO		O	NH	O
51	13	iPrCO		O	NOH	O
52	1	$C_{13}H_{27}CO$		O	NH	O
53	6	iPrCO		O	NH	O
54	6	$C_{17}H_{35}CO$		O	NH	O
55	10	iPrCO		O	NH	O
56	10	iPrCO		O	NH	O
57	10	iPrCO	H	O	NH	O
58	10	iPrCO		O	NH	O
59	15	tBuCO		O	NH	O
60	15	tBuCO	H	O	NH	O
61	13	$C_{17}H_{35}CO$		O	NH	O
62	13	MeCO	H	O	NH	O

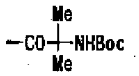
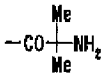
[Table 5]

実施例	k	R^1	R^2	Y	Z	W
63	13	tBuCO		O	NMe	O
64	13	iPrCO		O	NH	O
65	13	iPrCO	Me	O	NH	O
66	13	iPrCO		O	NH	O
67	13	iPrCO		O	NH	O
68	13	iPrCO		O	NH	O
69	13	iPrCO		O	NH	O
70	13	iPrCO		O	NH	O
71	13	tBuCO		O	NH	O
72	13	tBuCO		O	NH	O
73	13	iPrCO		O	NH	O
75	13	tBuCO		NH	NH	O
76	13	tBuCO	H	NH	NH	O
77	13	tBuCO	Me	NH	NH	O
78	13	tBuCO		NH	NH	O

[Table 6]

実施例	k	R^1	R^2	Y	Z	W
79	13	tBuCO		NH	NH	S
80	13	iPrCO		O	NH	O
81	13	tBuCO		O	NH	O
82	13	tBuCO		O	NH	O
83	13	tBuCO		O	NH	O
84	13	iPrCO		O	NH	O
85	13	tBuCO		O	NH	O
86	13	tBuCO		O	NH	O
87	13	iPrCO		O	NH	O
88	13	iPrCO		O	NH	O
89	13	iPrCO		O	NH	O
90	13	iPrCO		O	NH	O
91	10	iPrCO		O	NH	O
92	13	tBuCO		NH	NH	O
93	13	tBuCO		NH	NH	O
94	13	Boc	H	O	NH	O

[Table 7]

実施例	k	R^1	R^2	Y	Z	W
95	13	Boc		O	NH	O
96	13	H	H	O	NH	O
97	13	H		O	NH	O
98	13	H		O	NH	O
99	13			O	NH	O
100	13			O	NH	O
101	13			O	NH	O
102	13			O	NH	O
103	13			O	NH	O
104	13			O	NH	O

Example 13-O-(tert-butyldimethylsilyl)-2-N-pivaloyl D-erythro sphingosine (99 mg, 0.2mmol) was melted in dichloromethane (5 ml), pyridine (142 mg, 1.8mmol) was added, and it cooled at -78 **. After chloroformic acid trichloromethyl (22microl, 0.3mmol) was dropped at this solution, temperature up was carried out to -15 ** over 1 hour. The ammonia solution (2 ml) was dropped at this reaction mixture 25%, and temperature up was carried out to it to 15 ** over 3 hours. Water was added to reaction mixture, ethyl acetate extracted, and the solvent was distilled off after drying with magnesium sulfate. Column chromatography refined the residue and 3-O-(tert-butyldimethylsilyl)-1-O-carbamoyl 2-N-pivaloyl D-erythro sphingosine (72 mg) was obtained.

[0056]After melting the compound (72 mg, 0.13mmol) obtained here in pyridine (6 ml) and adding the acetonitrile (34 ml) solution of hydrofluoric acid bottom 2% of ice-cooling, it stirred for seven days at the room temperature. After it added saturated sodium bicarbonate water to reaction mixture and ethyl acetate subsequently extracted, it dried with magnesium sulfate. The solvent was distilled off, column chromatography refined the residue and 1-O-carbamoyl 2-N-pivaloyl D-erythro sphingosine (51 mg) was obtained.

^{1}H-NMR. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.6Hz,3H),1.19(s,9H),1.21-1.40(m,22H),2.03(m,2H),3.34(d,J=5.1Hz,1H),4.10(dd,J=3.8,11.8Hz,1H), 4.14(m,1H),4. 21 (m, 1H), 4.41 (dd, J= 7.6-11.7 Hz, 1H), 4.74 (bs, 2H), 5.45 (dd, J= 6.7-15.4 Hz, 1H), 5.74 (dt, J= 15.4, 6.7 Hz, 1H) and 6.29(d, J= 7.5-Hz, 1H)MS (SIMS) m/e:427$(M+H)^+$$C_{24}H_{46}N_2O_4$ (426)

[0057]The compound of Examples 2-63 was manufactured like the method of two to example 63

Example 1. The physical chemistry data of the ^{1}H-NMR spectrum of each compound, a mass spectrum, etc. is shown below. Compound ^{1}H-NMR of Example 2. ($CDCl_3$) delta(ppm):0.88(t,J=6.8Hz,3H),1.19(s,9H),1.20-1.43(m,22H),2.04(m,2H),2.71(d,J=4.5Hz,1H),4.19(d,J=5.3Hz,1H),4.24(m, 1H),4.30(dd,J=3,6,11.5Hz,1H),4.43(dd,J=7.8,11.6Hz,1H),5.47(dd,J=6.6,15.4Hz,1H),5.76(dt,J=15.4,6.7Hz, 1H, 6.05 (bs, 1H), 6.21 (d, J= 7.8 Hz, 1H) and 7.19(bs, 1H)MS(SIMS) m/e:505 $^{(M+Na)+}C_{28}H_{48}0_4$ (504) [0058]Compound ^{1}H-NMR of Example 3. ($CDCl_3$) delta. (ppm) : 0.88(t,J=7.0Hz,3H),1.17(s,9H),1.20-1.42(m,22H),1.90-2.08(m,4H),2.93(s,6H),3.16-3.34(m,4H),4.14(m,2H), 4.30 (m, 1H), 5.44 (dd, J= 6.7-15.3 Hz, 1H), 5.77 (dt, J= 15.3, 6.7 Hz, 1H), 6.05 (m, 1H) and 6.32(d, J= 8.0-Hz, 1H)MS(SIMS) m/e:512 $^{(M+H)+}C_{29}H_{57}N_30_4$ (511) [0059]Compound ^{1}H-NMR of Example 4. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.6Hz,1H),1.20(s,9H),1.22-1.40(m,22H),2.03(m,2H),2.82(s,6H),3.14(m,2H),3.45(m,1H),3.57(m,1H), 4.12-4.34 (m, 2H), 5.49 (dd, J= 6.4-15.3 Hz, 1H), 5.78 (dt, J= 15.3, 6.7 Hz, 1H), 5.92 (m, 1H), and 6.47(d, J= 7.6-Hz, 1H)MS(SIMS) m/e:498 $^{(M+H)+}C_{28}H_{55}N_30_4$ (497) [0060]Compound ^{1}H-NMR ($CDCl_3$) delta (ppm):0.88 (t, Hz [J= 6.7], 3H) of Example 5, 1.01 (d,J=6.4Hz,12H),1.18(s,9H),1.20-1.40(m,22H),2.02(m,2H),2.58(m,2H),3.01(m,2H),3.15(m,2H),3.78(m,1H),4. 01-4.26 (m, 3H), 4.42 (dt, J= 6.7-11.8 Hz, 1H), 5.44 (dd, J= 6.6-15.4 Hz, 1H), and 5.72(dt, J= 15.3, 6.7-Hz, 1H)MS(SIMS) m/e:554 $^{(M+H)+}C_{32}H_{63}N_3O_4$ (553) [0061]Compound ^{1}H-NMR of Example 6. ($CDCl_3$) delta(ppm):0.88(t,J=6.9Hz,3H),0.92(s,9H),1.19(s,9H),1.20-1.40(m,22H),1.41(m,2H),2.02(m,2H),3.05-3.25(m,2H),3.68(d, J=5.5Hz,1H),3.95-4.30(m,3H),4.42(dd,J=7.4,11.7Hz,1H),4.70(m,1H),5.44(dd,J=6.5,15.4Hz,1H),5.73(dt,J=15.4, 6.6 Hz, 1H, 6.41(d, J= 7.1-Hz, 1H)MS(SIMS) m/e:511 $^{(M+H)+}C_{30}H_{58}N_2O_4$ (510) [0062]Compound ^{1}H-NMR of Example 7. ($CDCl_3$) delta(ppm):0.88(t,J=6.5Hz,3H),1.17(s,9H),1.20-1.42(m,22H),2.02(m,2H),3.19(m,1H),4.19(m,1H),4.22-4.32(m,2H),4.52(dd, J=8.0,12.7Hz,1H),5.49(dd,J=6.7,15.4Hz,1H),5.76(dt,J=15.3,6.8Hz,1H),6.22(d,J=7.4Hz,1H),7.02(m,1H),7.70(m, 1H, 7.94 (m, 1H), 8.13 (bs, 1H) and 8.27(m, 1H)MS(SIMS) m/e:504$(M+H)^+C_{29}H_{49}N_3O_4$ (503) [0063]Compound ^{1}H-NMR of Example 8. ($CDCl_3$) delta(ppm):0.88(t,J=6.8Hz,3H),1.18(s,9H),1.20-1.40(m,22H),2.04(m,2H),4.21(m,1H),4.27-4.35(m,2H),4.52(dd,J=8.2,12. 4Hz,1H),5.50(dd,J=6.7,15.4Hz,1H),5.78(dt,J=15.4,6.5Hz,1H),6.17(d,J=7.8Hz,1H),7.45(bs,1H),8.22(m,1H),8.32 (m, 1H), 9.29(m, 1H)MS(SIMS) m/e:505 $^{(M+H)+}C_{28}H_{48}N_4O_4$ (504) [0064]Compound ^{1}H-NMR of Example 9. ($CDCl_3$) delta(ppm):0.88(t,J=6.9Hz,3H),1.17(s,9H),1.20-1.40(m,22H),2.03(m,2H),4.15-4.40(m,3H),4.50(dd,J=7.5,10.9Hz,1H),5. J= 6.3 Hz of 49(dd,J=6.5,15.4Hz,1H),5.78(dt,J=15.4,6.6Hz,1H),6.19(d,J=7.7Hz,1H),7.35(d,J=6.3Hz,1H),7.48(s,1H),8.47(d, 1HMS(SIMS) m/e:504 $^{(M+H)+}C_{29}H_{49}N_3O_4$ (503) [0065]Compound ^{1}H-NMR of Example 10. ($CDCl_3$) delta(ppm):0.88(t,J=7.1Hz,3H),1.17(s,9H),1.20-1.40(m,22H),2.03(m,2H),3.91(s,3H),4.12-4.33(m,3H),4.50(dd,J=4.7,12. 4Hz,1H),5.47(dd,J=6.5,15.4Hz,1H),5.75(dt,J=15.4,6.7Hz,1H),6.25(bd,J=6.2Hz,1H),6.73(d,J=8.9

Hz,1H),6.78(bs, 1H, 7.75 (bs, 1H) and 8.09(bs, 1H)MS(SIMS) m/e:534 $^{(M+H)^+}C_{29}H_{49}N_3O_4$ (533)
[0066]Compound ^{1}H-NMR of Example 11. ($CDCl_3$)
delta(ppm):0.88(t,J=6.7Hz,3H),1.18(s,9H),1.20-
1.40(m,22H),2.03(m,2H),2.82(d,J=4.1Hz,1H),4.27(m,2H),4.43(dd,J=2.
6,11.2Hz,1H),4.62(dd,J=3.6,11.1Hz,1H),5.54(J=6.3,15.3Hz,1H),5.78(dt,J=15.4,6.7Hz,1H),6.47(
d,J=7.6Hz, 1H, 8.77 (s, 1H), 12.2(bs, 1H)MS(SIMS) m/e:511$(M+H)^+C_{26}H_{46}N_4O_4S$ (510)
[0067]Compound ^{1}H-NMR of Example 12. ($CDCl_3$)
delta(ppm):0.88(t,J=6.8Hz,3H),1.18(s,9H),1.20-
1.40(m,22H),2.03(m,2H),3.12(d,J=3.1Hz,1H),4.20(m,1H),4.22(dd,J=3.
9,11.8Hz,1H),4.31(m,1H),4.53(dd,J=7.7,11.7Hz,1H),5.49(dd,J=6.6,15.4Hz,1H),5.77(dt,J=15.3,6.
7Hz,1H),6.
28(d,J=7.2Hz,1H),6.93(bs,1H),7.30(d,J=8.5Hz,1H),7.45(d,J=8.9Hz,1H),7.86(bs,1H),8.03(s,1H),
10.1(bs,1H)MS(SIMS) m/e:. 543$(M+H)^+C_{31}H_{50}N_4O_4$ (542) [0068]Compound ^{1}H-NMR of
Example 13. ($CDCl_3$) delta(ppm):0.88(t,J=6.6Hz,3H),1.16(s,9H),1.20-
1.40(m,22H),2.01(m,2H),4.12(m,2H),4.19(m,1H),4.43-4.54(m,3H),5.45(dd,
J=6.7,15.4Hz,1H),5.72(dt,J=15.4,6.7Hz,1H),5.96(m,1H),6.36(d,J=7.1Hz,1H),7.18-
7.30(m,2H),7.68(m,1H),8.55 (m.) 1HMS(SIMS) m/e:518$(M+H)^+C_{30}H_{51}N_3O_4$ (517)
[0069]Compound ^{1}H-NMR of Example 14. ($CDCl_3$)
delta(ppm):0.88(t,J=6.7Hz,3H),1.15(s,9H),1.20-
1.40(m,22H),2.02(m,2H),4.13(m,2H),4.21(m,1H),4.38(m,2H),4.43(dd,J=7.
7,11.6Hz,1H),5.38(m,1H),5.45(dd,J=6.7,15.4Hz,1H),5.73(dt,J=15.4,6.7Hz,1H),6.28(d,J=7.4Hz,1
H),7.29(m, 1H, 7.65 (m, 1H), 8.55(m, 2H)MS(SIMS) m/e:518$(M+H)^+C_{30}H_{51}N_3O_4$ (517)
[0070]Compound ^{1}H-NMR of Example 15. ($CDCl_3$) delta. (ppm) :
0.88(t,J=6.5Hz,3H),1.15(s,9H),1.20-1.44(m,22H),2.02(m,2H),3.72(m,1H),4.13-4.17(m,3H),4.34-
4.48(m,3H), 5.45 () [dd and] J= 6.6-15.4 Hz, 1H, 5.74 (dt, J= 15.3, 6.6 Hz, 1H), 6.29 (d, J= 7.4
Hz, 1H), 7.20 (m, 2H), and 8.57(m, 2H)MS(SIMS) m/e:518$(M+H)^+C_{30}H_{51}N_3O_4$ (517)
[0071]Compound ^{1}H-NMR of Example 16. ($CDCl_3$) delta. (ppm) :
0.88(t,J=6.6Hz,3H),1.17(s,9H),1.20-
1.40(m,22H),2.01(m,2H),2.97(m,2H),3.61(m,2H),4.06(m,2H),4.16(m,1H), 4.42(dd,J=7.3 11.9
Hz, 1H, 5.43 (dd, J= 6.6-15.3 Hz, 1H), 5.71 (dt, J= 15.4, 6.6 Hz, 1H), 6.39 (d, J= 7.2 Hz, 1H),
7.16 (m, 2H), 7.62 (m, 1H), and 8.53(m, 1H)MS(SIMS) m/e:532$(M+H)^+C_{31}H_{53}N_3O_4$ (531)
[0072]Compound ^{1}H-NMR of Example 17. ($CDCl_3$) delta(ppm) :
0.88(t,J=6.7Hz,3H),1.20(s,9H),1.20-
1.40(m,22H),2.03(m,2H),2.82(m,2H),3.37(m,1H),3.52(m,1H),4.10-4.37(m,
4H),5.40(bs,1H),5.47(dd,J=6.6,15.4Hz,1H),5.74(dt,J=15.6,6.3Hz,1H),6.37(d,J=7.0Hz,1H),6.83(s
,1H),7.59(s,1HMS(SIMS) m/e:. 521$(M+H)^+C_{29}H_{52}N_4O_4$ (520) [0073]Compound ^{1}H-NMR
($CDCl_3$) delta (ppm):0.86 (t, Hz [J= 6.4], 3H) of Example 18, 1.07 -
1.42(m,22H),1.15(s,9H),1.87-2.10(m,4H),3.02-3.23(m,3H),4.00(t,J=6.8Hz,2H),4.05-
4.27(m,3H),4.37(dd,J=7. 0,10.9Hz,1H),5.44(dd,J=6.3,15.4Hz,1H),5.62-
5.82(m,2H),6.32(d,J=7.4Hz,1H),6.92(bs,1H),7.03(bs,1H),7.03(bs, 1H, 7.52(bs, 1H)MS(SIMS)

m/e:535$(M+H)^+C_{30}H_{54}N_4O_4$ (534) [0074]Compound ^{1}H-NMR of Example 19. ($CDCl_3$-CD_3OD) delta. (ppm) : 0.81(t,J=6.5Hz,3H),0.96-1.40(m,22H),1.84-2.08(m,2H),4.02-4.50(m,6H),5.45(dd,J=6.4,15.5Hz,1H),5.71(dt, J= 15.5, 6.3 Hz, 1H and 7.08 (d, J= 5.4 Hz, 2H), 7.22-7.53 (m, 2H), 7.71 (d, J= 6.9 Hz, 2H) and 8.28(d, J= 5.4-Hz, 2H)MS(SIMS) m/e:538$(M+H)^+C_{32}H_{47}N_3O_4$ (537) [0075]Compound ^{1}H-NMR of Example 20. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.6Hz,3H),1.16(s,9H),1.22-1.40(m,22H),2.02(m,2H),3.56(bs,1H),4.11(m,2H),4.20(m,1H),4.36(m,2H), 4.45(dd,J=7. 6-11.8 Hz, 1H, 5.16 (m, 1H), 5.44 (dd, J= 6.6-15.3 Hz, 1H), 5.72 (dt, J= 15.4, 6.6-Hz, 1H), 6.37 (d, J= 7.0-Hz, 1H), and 7.26-7.40(m, 5H)MS(SIMS) m/e:517$(M+H)^+C_{31}H_{52}N_2O_4$ (516) [0076]Compound ^{1}H-NMR of Example 21. ($CDCl_3$) delta(ppm):0.88(t,J=6.7Hz,3H),1.17(s,9H),1.22-1.40(m,22H),2.02(m,2H),2.94(s,6H),3.69(d,J=5.1Hz,1H),4.08(m,2H),4. 19(m,1H),4.25(m,2H),4.45(dd,J=7.4,11.9Hz,1H),5.00(m,1H),5.44(dd,J=6.7,15.4Hz,1H),5.71(dt, J=15.3,6.5Hz, 1H, 6.40 (d, J= 7.0 Hz, 1H), 6.69 (d, J= 8.5 Hz, 2H), 7.14(d, J= 8.5-Hz, 2H)MS(SIMS) m/e:582$(M+Na)^+C_{33}H_{57}N_3O_4$ (559) [0077]Compound ^{1}H-NMR of Example 22. ($CDCl_3$) delta(ppm) : 0.87(t,J=6.4Hz,3H),1.13-1.44(m,22H),1.17(s,9H),1.19-2.11(m,2H),3.15-3.43(m,2H),3.35(bs,1H),3.60-3.82(m, 2H),4.06-4.36(m,4H),5.44(dd,J=6.3,15.4Hz,1H),5.62(t,J=5.7Hz,1H),5.73(dt,J=15.4,6.6Hz,1H),6.34(d,J=5. 8Hz, 1HMS(CI) m/e :. 471$(M+H)^+C_{26}H_{50}N_2O_5$ (471) [0078]Compound ^{1}H-NMR of Example 23. ($CDCl_3$) delta(ppm):0.88(t,J=6.7Hz,3H),1.19(s,9H),1.20-1.40(m,22H),1.72(m,2H),2.03(m,2H),2.25(m,1H),3.32(m,1H),3.39(dd,J=5. 0,16.1Hz,1H),3.71(m,2H),4.06-4.16(m,3H),4.39(dd,J=7.6,11.8Hz,1H),5.12(bs,1H),5.45(dd,J=6.6,15.4Hz,1H) and 5.73 (dt and J= 15.3.) 6.8 Hz, 1H, and 6.34(d, J= 7.2-Hz, 1H)MS(SIMS) m/e:485$(M+H)^+C_{27}H_{52}N_2O_5$ (484) [0079]Compound ^{1}H-NMR of Example 24. ($CDCl_3$) delta(ppm):0.86(t,J=6.4Hz,3H),1.06-1.40(m,22H),1.19(s,9H),1.40-1.73(m,4H),1.92-2.08(m,2H),2.32(t,J=7.0Hz,2H),3. 07-3.25(m,2H),3.66(s,3H),3.76(bs,1H),3.96-4.22(m,3H),4.40(m,1H),5.03(t,J=5.7Hz,1H),5.42(dd,J=6.3,15.4Hz, 1H, 5.70 (dt, J= 15.4, 6.5 Hz, 1H) and 6.38(d, J= 6.9-Hz, 1H)MS(SIMS) m/e:541$(M+H)^+C_{30}H_{56}N_2O_6$ (540) [0080]Compound ^{1}H-NMR of Example 25 (500 MHz) $CDCl_3$-CD_3ODdelta. (ppm) : 0.85(t,J=6.3Hz,3H),1.08-1.42(m,22H),1.15(s,9H),1.19-2.12(m,2H),4.16-4.48(m,4H),5.46(dd,J=5.5,15.5Hz, 1H, 5.78 (dt, J= 15.5, 6.5 Hz, 1H) and 6.51(bs, 1H)MS(SIMS) m/e:495$(M+H)^+C_{25}H_{46}N_6O_4$ (494) [0081]Compound ^{1}H-NMR of Example 26. ($CDCl_3$) delta(ppm):0.88(t,J=6.7Hz,3H),1.18(s,9H),1.20-1.40(m,22H),2.03(m,2H),2.46(m,2H),3.35(d,J=5.1Hz,1H),3.47(m,2H),4. 06-4.22(m,3H),4.36(dd,J=7.0,11.7Hz,1H),5.35(bs,1H),5.41-5.54(m,2H),5.68(bs,1H),5.72(dt,J=15.4,6.4Hz, 1H, 6.25(d, J= 7.1-Hz, 1H)MS(SIMS) m/e:498$(M+H)^+C_{27}H_{51}N_3O_5$ (497) [0082]Compound ^{1}H-NMR of Example 27. ($CDCl_3$) delta(ppm):0.88(t,J=6.9Hz,3H),1.17(s,9H),1.20-1.40(m,22H),1.75-1.92(m,2H),1.94-2.05(m,2H),2.90-3.03(m,2H),3.22(bs, 2H),3.24-3.36(m,2H),3.65(d,J=4.3Hz,1H),4.00-

4.25(m,3H),4.34(m,1H),5.44(dd,J=5.5,15.1Hz,1H),5.74(dt,J=15.1, 5.9 Hz, 1H, 6.11 (bs, 1H) and 6.37(d, J= 6.4-Hz, 1H)MS(SIMS) m/e:484$(M+H)^+C_{27}H_{53}N_3O_4$ (483) [0083]Compound ^{1}H-NMR of Example 28. ($CDCl_3$) delta(ppm):0.88(t,J=6.4Hz,3H),1.15(d,J=6.9Hz,6H),1.15-1.47(m,22H),1.93-2.11(m,2H),2.37(m,1H),3.21(bs,1H),4.04-4. J= 7.4 Hz of 28(m,3H),4.42(dd,J=6.8,11.1Hz,1H),5.01(bs,2H),5.45(dd,J=6.5,15.4Hz,1H),5.73(dt,J=15.4,6.6Hz,1H),6.06(d, 1HMS(SIMS) m/e:413$(M+H)^+C_{23}H_{44}N_2O_4$ (412) [0084]Compound ^{1}H-NMR of Example 29. ($CDCl_3$) delta(ppm):0.88(t,J=6.4Hz,3H),1.12-1.45(m,22H),1.15(d,J=7.0Hz,6H),1.94-2.12(m,2H),2.38(m,1H),2.74(bs,1H),3.00(d, J=4.5Hz,1H),3.15-3.47(m,2H),3.58-3.85(m,2H),4.08-4.32(m,4H),5.20(bs,1H),5.47(dd,J=6.3,15.4Hz,1H),5.75(dt, J= 15.4, 6.5 Hz, 1H and 6.09(bs, 1H)MS(SIMS) m/e:457$(M+H)^+C_{25}H_{48}N_2O_5$ (456) [0085]Compound ^{1}H-NMR of Example 30. ($CDCl_3$) delta(ppm):0.87(t,J=6.4Hz,3H),1.14(d,J=6.9Hz,6H),1.18-1.42(m,22H),1.60-1.80(m,2H),1.95-2.10(m,2H),2.37(m,1H),2. 48(bs,1H),3.22-3.42(m,3H),3.70(t,J=5.6Hz,2H),4.04-4.27(m,3H),4.36(dd,J=6.6,10.9Hz,1H),5.21(bs,1H),5.45 (dd, J = 6.3-15.4 Hz) 1H, 5.73 (dt, J= 15.4, 6.6 Hz, 1H), and 6.12(d, J= 7.4-Hz, 1H)MS(SIMS) m/e:471$(M+H)^+C_{26}H_{50}N_2O_5$ (470) [0086]Compound ^{1}H-NMR ($CDCl_3$) delta (ppm):0.88 (t, Hz [J= 6.9], 3H) of Example 31, 1.14 (d, J= 6.9 Hz, 6H) 1.20-1.47 (m, 22H), 1.59-1.86. (m, 4H), 2.37(m,1H),2.98(m,1H),3.13-3.31(m,2H),3.60-3.75(m,2H),4.00-4.26(m,3H),4.39(dd,J=7.1,9.3Hz,1H),4.95(bs, 1H, 5.46 (dd, J= 6.7-15.4 Hz, 1H), 5.75 (dt, J= 15.4, 6.5 Hz, 1H), and 6.12(d, J= 6.7-Hz, 1H)MS(SIMS) m/e:485$(M+H)^+C_{27}H_{52}N_2O_5$ (484) [0087]Compound ^{1}H-NMR of Example 32. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.4Hz,3H),1.08-1.50(m,22H),1.97-2.14(m,2H),2.30(s,3H),2.62(m,1H),3.99(m,1H),4.22-4.44(m,2H), 4.98(m,1H),5. 48 (dd, J= 8.3-15.3 Hz, 1H), 5.82 (dt, J= 15.3, 6.6 Hz, 1H), 6.64 (s, 1H), 7.09 (d, J= 8.8 Hz, 2H), and 7.24(d, J= 8.8 Hz, 2H)MS(SIMS) m/e:503$(M+H)^+C_{30}H_{50}N_2O_4$ (502) [0088]Compound ^{1}H-NMR of Example 33 (500 MHz) $CDCl_3$delta. (ppm) : 0.88(t,J=6.8Hz,3H),1.13(d,J=6.4Hz,3H),1.14(d,J=6.6Hz,3H),1.18-1.39(m,22H),1.96-2.08(m,2H),2.37(m,1H), 3.08(bs,1H),3. 80 (s, 3H), 4.11-4.24 (m, 2H), 4.24 (m, 1H), 4.48 (dd, J= 7.3-11.6 Hz, 1H), 5.49 (dd, J= 7.9-15.4 Hz, 1H), 5.70(dt,J=15.4,6.7Hz,1H),6.07(d,J=8.0Hz,1H),6.63(m,1H),6.87(d,J=7.9Hz,1H),6.90(bs,1H),7.09 (bs,1H),7.20 (m.) 1HMS(SIMS) m/e:519$(M+H)^+C_{30}H_{50}N_2O_5$ (518) [0089]Compound ^{1}H-NMR of Example 34. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.9Hz,3H),1.13(d,J=6.9Hz,3H),1.14(d,J=6.9Hz,3H),1.21-1.38(m,22H),2.00-2.08(m,2H),2.38(m,1H), 3.25(bs,1H),3. 87 (s, 3H), 4.11-4.25 (m, 2H), 4.28 (m, 1H), 4.50 (dd, J= 7.0, 11.7 Hz, 1H), 5.49 (dd, J= 6.7-15.4 Hz, 1H), 5.75(dt,J=15.4,6.7Hz,1H),6.09(d,J=7.9Hz,1H),6.87(d,J=8.0Hz,1H),6.96(m,1H),7.02(m,1H),7.30(m,1H),8.05(bs,1HMS(SIMS) m/e:. 519$(M+H)^+C_{30}H_{50}N_2O_5$ (518) [0090]Compound ^{1}H-NMR of Example 35. ($CDCl_3$) delta. (ppm) : 0.81(t,J=6.4Hz,3H),1.02-1.40(m,22H),1.04(d,J=6.8Hz,3H),1.06(d,J=6.8Hz,3H),1.87-2.05(m,2H),2.32(m,1H), 3.99-4.36(m,4H 5.40 (dd, J= 6.2-15.4 Hz, 1H), 5.68 (dt, J= 15.4, 6.6 Hz, 1H), 6.60 (m, 1H), 6.70 (d, J= 8.7-Hz, 2H), and 7.12(d, J= 8.7-Hz, 2H)MS(CI) m/e:505$(M+H)^+C_{29}H_{47}N_2O_5$ (504)

[0091]Compound ^{1}H-NMR of Example 36. ($CDCl_3$) delta. (ppm) : 0.83(t,J=6.4Hz,3H),1.05(d,J=6.9Hz,3H),1.07(d,J=6.8Hz,3H),1.12-1.40(m,22H),1.46(s,9H),1.90-2.07(m,2H), 2.33(m,1H),4. 02-4.38 (m, 4H), 5.41 (dd, J= 6.1-15.4 Hz, 1H), 5.70 (dt, J= 15.4, 6.6 Hz, 1H), 6.56 (d, J= 7.8 Hz, 1H), 6.90 (bs, 1H), and 7.24(s, 4H)MS(SIMS) m/e:504$(M+H)^+C_{29}H_{49}N_3O_4$ (503) [0092]Compound ^{1}H-NMR of Example 37. ($CDCl_3$-CD_3OD) delta. (ppm) : 0.82(t,J=6.4Hz,3H),1.04(d,J=6.6Hz,3H),1.07(d,J=6.6Hz,3H),1.05-1.41(m,22H),1.88-2.08(m,2H),2.33(m,1H), 2.51(s,3H),4. 05-4.40 (m, 4H), 5.42 (dd, J= 6.2-15.4 Hz, 1H), 5.71 (dt, J= 15.4, 6.6 Hz, 1H), 6.58 (d, J= 7.8 Hz, 1H), 7.45 (d, J= 8.8 Hz, 2H) and 7.86(d, J= 8.8-Hz, 2H)MS(SIMS) m/e:531$(M+H)^+C_{31}H_{50}N_2O_5$ (530) [0093]Compound ^{1}H-NMR of Example 38. ($CDCl_3$-CD_3OD) delta. (ppm) : 0.84(t,J=6.2Hz,3H),1.05(d,J=6.9Hz,3H),1.08(d,J=6.9Hz,3H),1.03-1.43(m,22H),1.09-2.09(m,2H),2.34(m,1H), 4.07-4.38(m,4H 5.43 (dd, J= 6.1-15.4 Hz, 1H), 5.73 (dt, J= 15.4, 6.6 Hz, 1H), 6.49 (d, J= 6.3-Hz, 1H) and 7.40-7.65(m, 4H)MS(SIMS) m/e:514$(M+H)^+C_{30}H_{47}N_3O_4$ (513) [0094]Compound ^{1}H-NMR of Example 39. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.4Hz,3H),1.11(d,J=6.8Hz,3H),1.13(d,J=6.9Hz,3H),1.05-1.45(m,22H),1.88-2.10(m,2H),2.38(m,1H), 2.86(bs,1H),4. 15-4.55 (m, 4H), 5.49 (dt, J= 15.5, 6.3 Hz, 1H), 5.77 (dd, J= 6.5-15.5 Hz, 1H), 6.08 (d, J= 7.7 Hz, 1H), 7.59 (d, J= 9.2 Hz, 2H), 8.12 (bs, 1H), and 8.18(d, J= 9.2-Hz, 2H)MS(SIMS) m/e:534$(M+H)^+C_{29}H_{47}N_3O_6$ (533) [0095]Compound ^{1}H-NMR of Example 40. ($CDCl_3$) delta(ppm):0.87(t,J=6.4Hz,3H),1.08-1.52(m,22H),1.10(d,J=6.8Hz,3H),1.12(d,J=6.8Hz,3H),1.37(t,J=7.1Hz,3H),1.90-2.11(m,2H),2.38(m,1H),4.14-4.57(m,4H),4.38(q,J=7.1Hz,2H),5.48(dd,J=6.3,15.5Hz,1H),5.75(dt,J=15.5,6.6Hz, 1H, 6.15 (d, J= 7.8 Hz, 1H), 7.46 (d, J= 8.7 Hz, 2H), 7.73 (bs, 1H), 7.98(d, J= 8.7-Hz, 2H)MS(SIMS) m/e:561$(M+H)^+C_{32}H_{52}N_2O_6$ (560) [0096]Compound ^{1}H-NMR of Example 41. ($CDCl_3$) delta(ppm):0.87(t,J=6.4Hz,3H),1.05(d,J=6.7Hz,6H),1.02-1.47(m,22H),1.90-2.10(m,2H),2.39(m,1H),3.22(bs,1H),3.92(s, 3H),4.13-4.23(m,3H),4.50(m,1H),5.50(dd,J=6.3,15.4Hz,1H),5.74(dt,J=15.4,6,5Hz,1H),6.05(d,J=7.2Hz,1H),7.06 (m, 1H), 7.54 (m, 1H), 8.02 (dd, J= 1.7, 8.0 Hz, 1H), 8.40 (d, J= 8.4 Hz, 1H), 10.60(s, 1H)MS(SIMS) m/e:547$(M+H)^+C_{31}H_{50}N_2O_6$ (546) [0097]Compound ^{1}H-NMR of Example 42. ($CDCl_3$) delta(ppm):0.87(t,J=6.4Hz,3H),1.11(d,J=6.8Hz,6H),1.12-1.48(m,22H),1.90-2.12(m,2H),2.34(m,1H),3.90-4.27(m,3H),4. J= 7.1 Hz of 34(d,J=5.8Hz,2H),4.42(m,1H),5.29(t,J=5.8Hz,1H),5.44(dd,J=6.3,15.5Hz,1H)5.71(dt,J=15.5,6.7 Hz,1H),6.17(d, 1H, 7.16-7.42(m, 5H)MS(CI) m/e503:$(M+H)^+C_{30}H_{50}N_2O_4$ (502) [0098]Compound ^{1}H-NMR of Example 43. ($CDCl_3$) delta(ppm):0.87(t,J=6.2Hz,3H),1.10(d,J=6.8Hz,6H),1.17-1,48(m,22H),1.89-2.11(m,2H),2.34(m,1H),4.08-4.29(m,3H),4. 29-4.48(m,3H),5.45(dd,J=5.9,15.3Hz,1H),5.60(t,J=5.9Hz,1H),5.73(dt,J=15.3,6.7Hz,1H),6.12(d,J=6.9Hz,1H), 7.19 (d, J = 5.3 Hz) 2H and 8.54(d, J= 5.3-Hz, 2H)MS(SIMS) m/e:604$(M+H)^+C_{34}H_{57}N_3O_6$ (603) [0099]Compound ^{1}H-NMR of Example 44. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.4Hz,3H),1.09(d,J=6.9Hz,3H),1.10(d,J=6.9Hz,3H),1.17-1.45(m,22H),1.92-

2.10(m,2H),2.32(m,1H), 3.40(bs,1H),4. 02-4.27 (m, 3H), 4.40 (m, 1H), 4.43 (d, J= 6.2 Hz, 2H), 5.31-5.51 (m, 2H), 5.70 (dt, J= 15.4, 6.8 Hz, 1H), 6. 12 (d, J= 7.2-Hz, 1H) and 7.17-7.43(m, 4H)MS(CI) m/e:537 $^{(M+H)^+}C_{30}H_{49}ClN_2O_4$ (536) [0100]Compound ^{1}H-NMR of Example 45. ($CDCl_3$-CD_3OD) delta. (ppm) : 0.87(t,J=6.3Hz,3H),1.11(d,J=6.8Hz,6H),1.12-1.45(m,22H),1.92-2.09(m,2H),2.33(s,3H),3.54(bs,1H),4.03-4.
26(m,3H),4.29(d,J=5.7Hz,2H),4.41(dd,J=6.8,11.1Hz,1H),5.24(t,J=5.5Hz,1H),5.44(dd,J=6.2,15.4 Hz,1H),5.71(dt, J= 15.4, 6.3 Hz, 1H, 6.19 (d, J= 7.1 Hz, 1H), and 7.14(s, 4H)MS(SIMS) m/e:517$(M+H)^+C_{31}H_{52}N_2O_4$ (516) [0101]Compound ^{1}H-NMR of Example 46. ($CDCl_3$) delta. (ppm) : 0.81(t,J=6.4Hz,3H),1.02-1.40(m,22H),1.04(d,J=6.8Hz,3H),1.06(d,J=6.8Hz,3H),1,87-2.05(m,2H),2.32(m,1H), 3.99-4.36(m,4H 5.40 (dd, J= 6.2-15.4 Hz, 1H), 5.68 (dt, J= 15.4, 6.6 Hz, 1H), 6.60 (m, 1H), 6.70 (d, J= 8.7 Hz, 2H), and 7.12(d, J= 8.7-Hz, 2H)MS(SIMS) m/e:561$(M+H)^+C_{32}H_{52}N_2O_6$ (560) [0102]Compound ^{1}H-NMR of Example 47. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.3Hz,3H),1.12(d,J=6.9Hz,6H),1.08-1.48(m,22H),1.91-2.12(m,2H),2.35(m,1H),2.80(t,J=7.0Hz,2H), 3.31-3.56(m,3H 3.99-4.26 (m, 3H), 4.38 (dd, J= 6.7-11.2 Hz, 1H), 4.92 (t, J= 5.3 Hz, 1H), 5.44 (dd, J= 6.3-15.4 Hz, 1H), 5.71 (dt, J= 15.4, 6.5 Hz, 1H), 6.13 (d, J= 7.3-Hz, 1H) and 7.10-7.38(m, 5H)MS(CI) m/e:517$(M+H)^+C_{31}H_{52}N_2O_4$ (516) [0103]Compound ^{1}H-NMR of Example 48. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.4Hz,3H),1.14(d,J=6.9Hz,6H),1.12-1.45(m,22H),1.93-2.11(m,2H),2.20-2.56(m,8H),3.18-3.38(m,2H), 3.64-3.79(m, 4H, 4.01-4.28 (m, 3H), 4.40 (dd, J= 6.4-15.4 Hz, 1H), 5.73 (dt, J= 15.4, 6.5-Hz, 1H) and 6.12(d, J= 7.1-Hz, 1H)MS(CI) m/e526$(M+H)^+C_{29}H_{55}N_3O_5$ (525) [0104]Compound ^{1}H-NMR of Example 49. ($CDCl_3$) delta. (ppm) : 0.83(t,J=6.6Hz,3H),1.05(d,J=6.7Hz,3H),1.07(d,J=6.7Hz,3H),1.05-1.45(m,22H),1.85-2.08(m,2H),2.33(m,1H), 4.05-4.50(m,4H 5.42 (dd, J= 6.3-15.5 Hz, 1H), 5.73 (dt, J= 15.5, 6.7 Hz, 1H), 6.57 (d, J= 8.0-Hz, 1H), 6.87 (d, J= 3.5-Hz, 1H), and 7.31(d, J= 3.5-Hz, 1H)MS(CI) m/e:496$(M+H)^+C_{26}H_{45}N_3O_4S$ (495) [0105]Compound ^{1}H-NMR ($CDCl_3$) delta (ppm):0.87 (t, Hz [J= 6.4], 3H) of Example 50, 1.00-1.45 (m, 22H), 1.11 (d, J= 6.8 Hz, 6H), 1.90-2.10. (m, 2H), and 2.35(m,1H),3.05(bs,1H),4.14-4.38(m,3H),4.50(m,1H),5.50(dd,J=6.2,15.5Hz,1H),5.75(dt,J=15.5,6.6Hz,1H),6.15 (d.) J= 7.7 Hz, 1H, 7.40 (m, 1H), 7.65 (m, 1H), 7.76 (d, J= 7.9-Hz, 1H), 7.83 (d, J= 8.4-Hz, 1H), and 8.15(s, 2H)MS(CI) m/e:540$(M+H)^+C_{32}H_{49}N_3O_4$ (539) [0106]Compound ^{1}H-NMR of Example 51. ($CDCl_3$) delta. (ppm) : 0.88(t,J=7.0Hz,3H),1.07(d,J=6.9Hz,2H),1.09(d,J=6.9Hz,2H),1.18-1.40(m,22H),1.97-2.09(m,2H),2.32(m,1H), 4.13-4.25(m,2H 4.34 (dd, J= 3.2-11.6 Hz, 1H), 4.41 (dd, J= 7.6-11.6 Hz, 1H), 4.66 (d, J= 15.9 Hz, 1H), 4.75 (d, J= 15.9 Hz) J= 4.7 Hz of 1H),5.48 (dd,J=6.3,15.4Hz,1H),5.75(dt,J=15.4,6.7Hz,1H),6.19(d,J=7.6Hz,1H),7.26(d,J=4.7Hz,2H),8.43(d, 2HMS(SIMS) m/e:520 $^{(M+H)^+}C_{29}H_{49}N_3O_5$ (519) [0107]Compound ^{1}H-NMR of Example 52. ($CDCl_3$) delta(ppm):0.88(t,J=6.8Hz,3H),1.20-1.36(m,20H),1.60(m,2H),1.71(d,J=6.4Hz,1H),2.17(m,2H),4.10-4.19(m,2H),4.21(m, 1H),4.27(m,1H),4.35(d,J=2.9Hz,1H),5.49(m,1H),5.76(m,1H),6.28(bd,1H),6.38(bd,1H),7.23(d,J= 5.6Hz,1H),8.53 (d, J= 5.3 Hz, 1H) [0108]Compound ^{1}H-NMR of Example 53. ($CDCl_3$) delta. (ppm) :0.87(t,J=6.3Hz,3H),1.11(d,J=6.8Hz,6H),1.05-1.50(m,22H),1.90-

2.16(m,2H),2.34(m,1H),3.98-4.52(m,6H),5. 34-5.60 (m.) 2H, 5.73 (dt, J= 15.4, 6.8 Hz, 1H), 6.10 (d, J= 7.1 Hz, 1H), 7.19 (d, J= 5.5-Hz, 1H) and 8.55(d, J= 5.5-Hz, 1H)MS(CI) m/e406$(M+H)^+C_{22}H_{35}N_3O_4$ (405) [0109]Compound ^{1}H-NMR of Example 54 (500 MHz) $CDCl_3$delta(ppm): 0.88(t,J=6.9Hz,6H),1.18-1.40(m,34H),1.53-1.69(m,4H),1.96-2.10(m,2H),2.11-2.22(m,2H),3.07(bs,1H),4.11-4. 20(m,2H),4.25(m,1H),4.34-4.44(m,3H),5.31(t,J=6.1Hz,1H),5.47(dd,J=6.6,15.3Hz,1H),5.74(dt,J=15.3,6.7Hz, 1H, 6.01 (d, J= 8.0 Hz, 1H), 7.20 (d, J= 5.8 Hz, 2H), 8.57(d, J= 5.8-Hz, 2H)MS(SIMS) m/e:602$(M+H)^+C_{36}H_{63}N_3O_4$ (601) [0110]Compound ^{1}H-NMR of Example 55. ($CDCl_3$) delta(ppm):0.87(t,J=6.4Hz,3H),1.10(d,J=6.8Hz,6H),1.12-1.47(m,16H),1.90-2.13(m,2H),2.33(m,1H),3.40(bs,1H),4.04-4. 50(m,6H),5.44(dd,J=6.2,15.5Hz,1H),5.57-5.82(m,2H),6.14(d,J=7.3Hz,1H),7.23(d,J=5.8Hz,2H),8.53(d,J=5.8Hz,2HMS(SIMS) m/e:. 462$(M+H)^+C_{26}H_{43}N_3O_4$ (461) [0111]Compound ^{1}H-NMR of Example 56. ($CDCl_3$) delta(ppm):0.87(t,J=6.3Hz,3H),1.10(d,J=6.7Hz,6H),1.10-1.46(m,16H),1.90-2.10(m,2H),2.33(m,1H),3.35(bs,1H),3.90(s, J= 8.1 Hz of 3H),4.04-4.27(m,3H),4.31-4.51(m,3H),5.33-5.65(m,2H),5.72(dt,J=15.2,6.5Hz,1H),6.14(d,J=7.2Hz,1H),7.33(d, 2H, 7.99(d, J= 8.1-Hz, 2H)MS(SIMS) m/e:519$(M+H)^+C_{29}H_{46}N_2O_6$ (518) [0112]Compound ^{1}H-NMR of Example 57. ($CDCl_3$) delta(ppm):0.88(t,J=6.3Hz,3H),1.15(d,J=6.9Hz,6H),1.11-1.46(m,16H),1.94-2.13(m,2H),2.37(m,1H),3.17(bs,1H),4.06-4. J= 7.1 Hz of 29(m,3H),4.39(dd,J=6.8,11.1Hz,1H),4.74(bs,2H),5.45(dd,J=6.5,15.3Hz,1H),5.74(dt,J=15.3,6.7Hz,1H),6.06(d, 1HMS(CI) m/e:371$(M+H)^+C_{20}H_{38}N_2O_4$ (370) [0113]Compound ^{1}H-NMR of Example 58. ($CDCl_3$) delta(ppm):0.86(t,J=6.4Hz,3H),1.12(d,J=6.9Hz,6H),1.13-1.43(m,16H),1.90-2.08(m,2H),2.21(s,6H),2.36(m,1H),2.40(t, J=6.3Hz,2H),2.47(bs,1H),3.24(m,2H),4.00-4.23(m,3H),4.39(dd,J=6.0,11.1Hz,1H),5.44(dd,J=6.4,15.4Hz,1H), 5.58 (m, 1H), 5.71 (dt, J= 15.4, 6.4-Hz, 1H) and 6.29(d, J= 7.2-Hz, 1H)MS(CI) m/e:442$(M+H)^+C_{24}H_{47}N_3O_4$ (441) [0114]Compound ^{1}H-NMR of Example 59. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.6Hz,3H),1.19(s,9H),1.20-1.40(m,26H),2.03(m,2H),3.32(d,J=5.4Hz,1H),4.10(dd,J=3.8,11.9Hz,1H), 4.14(m,1H),4. 21 (m, 1H), 4.41 (dd, J= 7.6-11.8 Hz, 1H), 4.69 (bs, 2H), 5.45 (dd, J= 6.7-15.4 Hz, 1H), 5.74 (dt, J= 15.3, 6.8 Hz, 1H) and 6.29(d, J= 7.4-Hz, 1H)MS(SIMS) m/e:455$(M+H)^+C_{26}H_{50}N_2O_4$ (454) [0115]Compound ^{1}H-NMR of Example 60. ($CDCl_3$) delta(ppm):0.88(t,J=6.8Hz,3H),1.15(s,9H),1.20-1.40(m,26H),2.02(m,2H),3.33(bs,1H),4.13(m,2H),4.20(m,1H),4.32-4.49(m, J= 7.7 Hz of 3H),5.25(m,1H),5.44(dd,J=6.7,15.4Hz,1H),5.73(dt,J=15.4,6.6Hz,1H),6.28(d,J=7.4Hz,1H),7.28(m,1H),7.63(d, 1H, 8.55(m, 2H)MS(SIMS) m/e:546$(M+H)^+C_{32}H_{55}N_3O_4$ (545) [0116]Compound ^{1}H-NMR of Example 61. ($CDCl_3$) delta(ppm):0.88(t,J=6.6Hz,6H),1.08-1.43(m,52H),1.93-2.10(m,2H),2.17(t,J=7.5Hz,2H),2.98(bs,1H),4.10-4.44(m,6H),5. 34(t,J=6.3Hz,1H),5.47(dd,J=6.6,15.6Hz,1H),5.74(dt,J=15.6,6.6Hz,1H),6.00(d,J=6.9Hz,1H),7.20(d,J=5.5Hz, 2H, 8.57(d, J= 5.5-Hz, 2H)MS(SIMS) m/e:700$(M+H)^+C_{43}H_{77}N_3O_4$ (699) [0117]Compound ^{1}H-NMR of Example 62. ($CDCl_3$) delta. (ppm) :0.87(t,J=6.4Hz,3H),1.08-

1.45(m,22H),1.93-2.11(m,2H),2.00(s,3H),3.14(bs,1H),4.03-4.28(m,3H),4.34(dd,J=6.2-10.6Hz, 1H, 4.86 (bs, 2H), 5.47 (dd, J= 6.2-15.4 Hz, 1H), 5.74 (dt, J= 15.4, 6.5 Hz, 1H) and 6.13(d, J= 6.8-Hz, 1H)MS(SIMS) m/e:385$(M+H)^+C_{21}H_{40}N_2O_4$ (384) [0118]Compound ^{1}H-NMR ($CDCl_3$) delta (ppm):0.88 (t, Hz [J= 6.6], 3H) of Example 63, 1.18 (s, 9H), 1.20-1.44 (m, 22H), 1.90-2.12 (m, 4H), 2.88 (d, J= 4.9 Hz, 3H), 2.90 (s, 6H), 2.96-3.54 (m, 4H), 4.12-4.40 (m, 3H), 5.48 (m, 1H) and 5.78 (dt, J= 15.2, 6.6 Hz, 1H), 6.33(m, 1H)MS(SIMS) m/e:526$(M+H)^+C_{30}H_{59}N_3O_4$ (525) [0119]Compound ^{1}H-NMR of Example 64. ($CDCl_3$) delta. (ppm) : 0.79(t,J=6.3Hz,3H),1.00(d,J=6.8Hz,3H),1.03(d,J=6.8Hz,3H),1.00-1.40(m,22H),1.84-2.05(m,2H),2.04(s,3H), 2.30(m,1H),3. 98-4.35 (m, 4H), 5.38 (dd, J= 6.3-15.4 Hz, 1H), 5.66 (dt, J= 15.4, 6.6 Hz, 1H), 6.72 (d, J= 7.9 Hz, 1H), 7.23 (d, J= 8.9 Hz, 2H) and 7.35(d, J= 8.9-Hz, 2H)MS(SIMS) m/e:546$(M+H)^+C_{31}H_{51}N_3O_5$ (545) [0120]Example 653-O-(tert-butyldimethylsilyl)-2-N-isobutyryl D-erythro sphingosine (30 mg, 0.062mmol) is melted in a tetrahydrofuran (0.5 ml), Triethylamine (one drop) and methyliso cyanate (90 mg, 0.92mmol) were added, and it stirred at 60 ** for 6 hours. The reaction mixture was melted after concentration, the residue was melted in the tetrahydrofuran (0.5 ml) by decompression, tetrabutylammonium fluoride (tetrahydrofuran 1M solution, 0.80 ml) was added, and it stirred at the room temperature for 4 hours. Column chromatography refined the residue and 1-O-methylamino carbonyl 2-N-isobutyryl D-erythro sphingosine (16 mg) was obtained. ^{1}H-NMR. ($CDCl_3$) delta. (ppm) : 0.83(t,J=6.4Hz,3H),1.12(d,J=6.9Hz,6H),1.08-1.45(m,22H),1.90-2.10(m,2H),2.36(m,1H),2.77(d,J=4.9Hz,3H), 3.58(bs,1H),3. 98-4.25 (m, 3H), 4.38 (dd, J= 6.8-11.2 Hz, 1H), 4.96 (m, 1H), 5.44 (dd, J= 6.3-15.4 Hz, 1H), 5.71 (dt, J= 6.4-15.4 Hz, 1H) and 6.21(d, J= 7.1-Hz, 1H)MS(CI) m/e:427$(M+H)^+C_{24}H_{46}N_2O_4$ (426) [0121]The compound of Examples 65-71 was manufactured like the method of 66 to example 72 Example 65. The physical chemistry data of the ^{1}H-NMR spectrum of each compound, a mass spectrum, etc. is shown.

Compound ^{1}H-NMR of Example 66. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.4Hz,3H),1.12(d,J=6.9Hz,3H),1.13(d,J=6.8Hz,3H),1.13-1.46(m,22H),1.92-2.11(m,2H),2.37(m,1H), 3.17(bs,1H),4. 10-4.37 (m, 3H), 4.47 (dd, J= 6.8-10.8 Hz, 1H), 5.48 (dd, J= 6.3-15.4 Hz, 1H), 5.75 (dt, J= 15.4, 6.9 Hz, 1H), 6.14 (d, J= 7.6 Hz, 1H), 7.07 (m, 1H), 7.13 (bs, 1H), and 7.23-7.44(m, 4H)MS(CI) m/e489$(M+H)^+C_{29}H_{48}N_2O_4$ (488) [0122]Compound ^{1}H-NMR of Example 67. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.3Hz,3H),1.11(d,J=6.9Hz,3H),1.13(d,J=6.9Hz,3H),1.05-1.42(m,22H),1.91-2.10(m,2H),2.38(m,1H), 3.00(m,1H),4. 16-4.57 (m, 4H), 5.48 (dd, J= 6.3-15.4 Hz, 1H), 5.78 (dt, J= 15.4, 6.5 Hz, 1H), 6.09 (d, J= 7.8 Hz, 1H), 7.25-7. 49 (m, 2H), 7.49-7.65 (m, 2H), and 7.72(bs, 1H)MS(CI) m/e557$(M+H)^+C_{30}H_{47}F_3N_2O_4$ (556) [0123]Compound ^{1}H-NMR of Example 68. ($CDCl_3$) delta. (ppm) : 0.87(t,J=6.4Hz,3H),1.11(d,J=6.8Hz,3H),1.13(d,J=6.8Hz,3H),1.04-1.46(m,22H),1.92-2.12(m,2H),2.37(m,1H), 3.21(bs,1H),3. 78 (s, 3H), 4.10-4.35 (m, 3H), 4.46 (dd, J= 6.7-10.9 Hz, 1H), 5.47 (dd, J= 6.3-15.4 Hz, 1H), 5.74 (dt, J= 15.4, 6.6 Hz, 1H), 6.11 (d, J= 7.4-Hz, 1H), 6.74-6.94 (m, 2H), and 7.14-7.38(m, 2H)MS(CI) m/e:519$(M+H)^+C_{30}H_{50}N_2O_5$ (518) [0124]Compound ^{1}H-NMR of Example 69. ($CDCl_3$) delta. (ppm) :

0.88(t,J=6.4Hz,3H),1.12(d,J=6.8Hz,3H),1.14(d,J=6.8Hz,3H),1.10-1.45(m,22H),1.92-2.12(m,2H),2.38(m,1H), 3.00(bs,1H),3. 87 (s, 3H), 4.14-4.38 (m, 3H), 4.49 (m, 1H), 5.49 (dd, J= 6.3-15.4 Hz, 1H), 5.76 (dt, J= 15.4, 6.6 Hz, 1H), 6.07 (d, J= 7.8 Hz, 1H), 7.22 (bs, 1H), 7.38 (m, 1H), 7.62-7.81 (m, 2H), and 7.98(s, 1H)MS(SIMS) m/e:547$(M+H)^+C_{31}H_{50}N_2O_6$ (546)

[0125]Compound ^{1}H-NMR of Example 70. ($CDCl_3$) delta. (ppm) :
0.87(t,J=6.4Hz,3H),1.06(t,J=6.8Hz,3H),1.09(t,J=6.8Hz,3H),1.11-1.48(m,22H),1.90-2.12(m,2H),2.32(m,1H), 4.08-4.43(m,4H 5.42 (dd, J= 5.9-15.4 Hz, 1H), 5.74 (dt, J= 15.4, 6.7 Hz, 1H), 6.14 (d, J= 7.7-Hz, 1H), 7.47-7.71 (m, 3H), and 7.95-8.09(m, 2H)MS(SIMS) m/e:575$(M+Na)^+C_{29}H_{48}N_2O_6S$ (552)

[0126]Compound ^{1}H-NMR of Example 71. ($CDCl_3$) delta(ppm):0.88(t,J=6.9Hz,3H),1.21(s,9H),1.20-1.40(m,22H),2.04(m,2H),3.55(d,J=7.0Hz,1H),4.24(m,2H),4.49(m,2H),5.53(dd,J=5.9,15.5Hz,1H),5.82(dt,J=15.6,6.7Hz,1H),6.58(d,J=7.4Hz,1H),7.51(m,2H),7.62(m,1H), 7.85(m,1H),8.31 (s, 1H)

[0127]Compound ^{1}H-NMR of Example 72. ($CDCl_3$) delta(ppm):0.88(t,J=6.7Hz,3H),1.18(s,9H),1.20-1.40(m,22H),1.29(t,J=7.1Hz,3H),2.02(m,2H),3.20(bs,1H),3.39(d,J=5. 1Hz,2H),4.05-4.25(m,3H),4.23(q,J=7.2Hz,2H),4.45(dd,J=6.2,11.1Hz,1H),5.31(m,1H),5.45(dd,J=6.6,15.4Hz, 1H, 5.74(dt,J=15.4,6.5Hz,1H),6.26(d,J=6.7Hz,1H)

[0128]In the tetrahydrofuran (1 ml) solution of example 734-(methylthio) aniline (56 mg, 0.4mmol). After adding 2 di-tert-butyl carbonate (109 mg, 0.50mmol) and adding N,N-dimethylamino pyridine (49 mg, 0.4mmol) subsequently, it stirred for 30 minutes at the room temperature. The tetrahydrofuran (1 ml) solution of 3-O-(tert-butyldimethylsilyl)-2-N-isobutyryl D-erythro sphingosine (48 mg, 0.10mmol) was added to this reaction mixture, and it stirred at the room temperature for 12 hours. It condensed under decompression of this reaction mixture, column chromatography refined the residue, and 1-O-[4-(methylthio) anilinocarbonyl]-2-N-isobutyryl 3-O-(tert-butyldimethylsilyl)-D-erythro sphingosine (30 mg) was obtained.

^{1}H-NMR ($CDCl_3$) delta (ppm):0.00 (s, 3H), 0.03. (s, 3H),
0.87(t,J=6.7Hz,3H),0.90(s,9H),1.09(d,J=6.9Hz,3H),1.11(d,J=6.9Hz,3H),1.12-1.55(m,22H),1.92-2.12(m,2H), 2.31(m,1H),2. 45 (s, 3H), 4.10-4.30 (m, 3H), 4.48 (m, 1H), 5.41 (dd, J= 6.2-15.5 Hz, 1H), 5.67 (dt, J= 15.5, 6.7 Hz, 1H), 5.85 (d, J= 8.1 Hz, 1H), 6.95 (s, 1H), and 7.15-7.40 (m, 4H)

[0129]The compound (30 mg, 0.046mmol) obtained here was melted in the tetrahydrofuran (1 ml), the bottom tetrabutylammonium fluoride of ice-cooling (0.5 ml as 1M solution) was added, and it stirred under the temperature for 5 hours. Saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. With magnesium sulfate, after desiccation, it condensed, column chromatography refined the residue, and 1-O-[4-(methylthio) anilinocarbonyl]-2-N-isobutyryl D-erythro sphingosine (14 mg) was obtained.

^{1}H-NMR. ($CDCl_3$-CD_3OD) delta. (ppm) :
0.81(t,J=6.3Hz,3H),1.02(d,J=6.7Hz,3H),1.05(d,J=6.9Hz,3H),0.90-1.40(m,22H),1.84-2.05(m,2H),2.32(m,1H), 3.20(s,3H),3. 95-4.38 (m, 4H), 5.39 (dd, J= 6.2-15.3 Hz, 1H), 5.68 (dt, J= 15.3, 6.6 Hz, 1H), 6.65 (d, J= 7.9 Hz, 1H), 7.15 (d, J= 8.6 Hz, 2H) and 7.27(d, J= 8.6-Hz, 2H)MS(SIMS) m/e:535$(M+H)^+C_{30}H_{50}N_2O_4S$ (534)

[0130]Example 753-O-(tert-

butyldimethylsilyl)-2-N-pivaloyl D-erythro sphingosine (0.90 mg, 1.8mmol) is melted in the mixed solvent of dimethyl sulfoxide (12 ml) and a tetrahydrofuran (12 ml), It ice-cooled, after adding triethylamine (6 ml). The sulfur trioxide pyridine complex (2.84 g, 18mmol) was added to this solution, and it stirred for 30 minutes. Saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. The extract was condensed after desiccation with magnesium sulfate, column chromatography refined the residue, and (1'S,2'R,3'E)-N-[2-(tert-butyldimethylsilyloxy)-1-formyl-3-heptadecenyl] PIBARU amide (aldehyde object) (0.80g) was obtained.

^{1}H-NMR. ($CDCl_3$) delta. (ppm) :0.00(s,3H),0.01(s,3H),0.86(s,9H),0.89(t,3H),1.23(s,9H),1.23-1.38(m,22H),2.08(m,2H),4.48-4.57(m,2H),5.67 (dd and J= 6.0.)
15.4Hz,1H),5.89(dt,J=15.2,7.0Hz,1H),6.52(d,J=6.1Hz,1H),9.71(s,1H) [0131]The aldehyde object (0.86 g,1.8mmol) and hydroxylamine hydrochloride (0.47 g,6.7mmol) which were obtained here were melted in the tetrahydrofuran (12 ml), N,N-diisopropylethylamine (1.16 g, 9.0mmol) was added, and it stirred at the room temperature for 3 hours. Saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. Condense after desiccation with magnesium sulfate and column chromatography refines a residue, (1'S,2'R,3'E)-N-[-(tert-butyldimethylsilyloxy)-1-hydroxy imino methyl-3-heptadecenyl] PIBARU amide (hydroxylimine object) (0.88g) was obtained.

[0132]The hydroxylimine object (3.18 g, 6.2mmol) acquired here was melted in the tetrahydrofuran (50 ml), and under ice-cooling, an acetic anhydride (0.70 ml) and pyridine (0.70 ml, 8.7mmol) were added one by one, and were stirred for 20 minutes. Water was added to reaction mixture and ethyl acetate extracted. Condense after desiccation with magnesium sulfate and column chromatography refines a residue, (1'S,2'R,3'E)-N-[1-acetoxy imino methyl-2-(tert-butyldimethylsilyloxy)-3-heptadecenyl] PIBARU amide (acetoxyimine object) (2.53g) was obtained.

^{1}H-NMR. ($CDCl_3$) delta(ppm):0.01(s,3H),0.04(s,3H),0.88(s,9H),0.88(t,3H),1.21(s,9H),1.21-1.40(m,22H),2.03(m,2H),2.16(s,3H),4.40(m,
1H),4.66(m,1H),5.43(dd,J=6.7,15.5Hz,1H),5.74(dt,J=15.4,6.8Hz,1H),6.34(d,J=7.3Hz,1H),7.75(d,J=4.6Hz,1H) [0133]In the ethanol (200 ml) solution of the acetoxyimine object (2.53 g, 4.6mmol) acquired here. After adding molybdic acid (5.48 g,37.5mmol), sodium borohydride (4.79 g, 127mmol) was added under -30 ** cooling, temperature up was carried out to 0 **, and it stirred at the temperature for 48 hours. The ammonia solution was added to reaction mixture 10%, and ethyl acetate extracted. With magnesium sulfate, after desiccation, it condensed, column chromatography refined the residue, and (1'S,2'R,3'E)-N-[1-aminomethyl 2-(tert-butyldimethylsilyloxy)-3-heptadecenyl] PIBARU amide (amine object) (1.32g) was obtained.

[0134]In next, the dichloromethane (5 ml) solution of 4-dimethylaminopyridine (73 mg, 0.6mmol). After adding 2 di-tert-butyl carbonate (0.15 mg, 0.7mmol) and adding 4-pyridylmethylamine (65 mg, 0.6mmol) subsequently, it stirred for 30 minutes at the room temperature. The amine object (99 mg, 0.2mmol) acquired by this reaction mixture at the previous reaction was added, and it stirred at the room temperature for 5 hours. Column

chromatography refines a residue after condensing reaction mixture, (-- 1' -- S,2' -- R,3' -- E --) - N - [-- two - (tert-butyldimethylsilyloxy)-1-[-- [-- three - (4-pyridyl methyl) -- ureido --] -- methyl --]-3-heptadecenyl --] -- PIBARU -- amide (ureido object) (94 mg) -- having obtained . [0135]The ureido object (93 mg, 0.15mmol) acquired here was melted in the tetrahydrofuran (1.8 ml), the bottom tetrabutylammonium fluoride of ice-cooling (1.8 ml as 1M solution) was added, and it stirred for 20 minutes under the temperature. Saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. magnesium sulfate -- desiccation -- after -- condensing -- a residue -- column chromatography -- refining -- (-- 1' -- S,2' -- R,3' -- E --) - N - [-- two - hydroxy- -- one - [-- [-- three - (4-pyridyl methyl) -- ureido --] -- methyl --]-3-heptadecenyl --] -- PIBARU -- amide (94 mg) -- having obtained . ^{1}H-NMR. ($CDCl_3$) delta(ppm):0.88(t,J=6.7Hz,3H),1.12(s,9H),1.20-1.40(m,22H),2.02(m,2H),3.27(dt,J=4.9,14.4Hz,1H),3.50(m,1H),3.87(m, 1H),4.10(m,1H),4.35(m,1H),5.46(dd,J=6.6,15.4Hz,1H),5.58(bs,1H),5.64(bs,1H),5.73(dt,J=15.4, 6.6Hz,1H),6.65 (d, J= 6.4 Hz, 1H), 7.19 (d, J= 4.6 Hz) and 8.51(bs, 1H)MS(SIMS) m/e:517$(M+H)^+C_{30}H_{52}N_4O_3$ (516) [0136]The compound of Examples 76-78 was manufactured like the method of 76 to example 78 Example 75. The physical chemistry data of the ^{1}H-NMR spectrum of each compound, a mass spectrum, etc. is shown. Compound ^{1}H-NMR of Example 76. ($CDCl_3$) delta. (ppm) :0.88(t,J=7.1Hz,3H),1.19(s,9H),1.20-1.40(m,22H),2.04(m,2H),3.25(m,1H),3.50(m,1H),3.72(bs,1H),3.91(m,1H), and 4.11 (m.) 1H, 4.59 (bs, 2H), 5.28 (bs, 1H), 5.47 (dd, J= 6.6-15.4 Hz, 1H), 5.75 (dt, J= 15.4, 6.8 Hz, 1H) and 6.61(bs, 1H)MS(SIMS) m/e:426$(M+H)^+C_{24}H_{47}N_3O_3$ (425) [0137]Compound ^{1}H-NMR of Example 77. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.8Hz,3H),1.18(s,9H),1.20-1.40(m,22H),2.03(m,2H),2.76(d,J=4.9Hz,1H),3.25(dt,J=14.4,4.9Hz,1H), 3.54(m,1H),3. 90 (m, 1H), 4.02 (m, 1H), 4.09 (m, 1H), 4.59 (bs, 1H), 4.96 (t, J= 5.9 Hz, 1H), 5.47 (dd, J= 6.5-15.4 Hz, 1H), 5.74 (dt, J= 15.4, 6.6 Hz, 1H), and 6.71(d, J= 6.5-Hz, 1H)MS(SIMS) m/e:462$(M+Na)^+C_{25}H_{49}N_3O_3$ (439) [0138]Compound ^{1}H-NMR of Example 78. ($CDCl_3$) delta(ppm):0.88(t,J=6.8Hz,3H),1.18(s,9H),1.20-1.40(m,22H),1.37(J=7.1Hz,3H),2.01(m,2H),3.36(dt,J=14.5,4.9Hz,1H), 3.56(m,1H),3.94(m,1H),4.17(m,1H),4.34(m,2H),5.50(dd,J=6.4,15.5Hz,1H),5.77(dt,J=15.0,6.7Hz ,1H),6.01(bs, 1H, 6.58 (d, J= 7.2 Hz, 1H), 7.45 (d, J= 8.5 Hz, 1H), 7.68 (bs, 1H), 7.95(d, J= 8.7-Hz, 1H)MS(SIMS) m/e:596$(M+Na)^+C_{33}H_{55}N_3O_5$ (573) [0139]Example 79. (1'S, 2'R, 3'E)-N-[-1-aminomethyl 2-. (tert-butyldimethylsilyloxy) Pyridine (31 mg, 0.4mmol) is added to the tetrahydrofuran (4 ml) solution of]-3-heptadecenyl] PIBARU amide (amine object) (99 mg, 0.2mmol), -It warmed to -20 ** over 1 hour after dropping bottom chloro CHIONOGI acid phenyl of 78 ** cooling (41microl, 0.3mmol). Saturated sodium bicarbonate water was added to reaction mixture, and ethyl acetate extracted. Condense after desiccation with magnesium sulfate and column chromatography refines a residue, (1'S,2'R,3'E)-N-[2-(tert-butyldimethylsilyloxy)-1-(phenoxythiocarbonyl aminomethyl)-3-heptadecenyl] PIBARU amide (42 mg) was obtained. ^{1}H-NMR. ($CDCl_3$) delta(ppm):0.09(s,3H),0.88(t,J=7.1Hz,3H),0.94(s,9H),1.22(s,9H),1.20-1.43(m,22H),2.06(m,2H),3.78-3.92(m,2H),4.10(m,

1H),4.34(m,1H),5.46(dd,J=6.6,15.4Hz,1H),5.76(dt,J=15.4,6.7Hz,1H),6.32(d,J=7.7Hz,1H),7.04(d,J=7.9Hz,1H), 7.25 (d, J = 7.9 Hz) 1H),7.38(d,J=7.9Hz,1H),7.89(m,1H) [0140]After melting the compound (86 mg, 0.14mmol) obtained here in dimethyl sulfoxide (1 ml), 4-pyridylmethylamine (15microl) was added and it stirred at the room temperature for 5 hours. Water was added to reaction mixture and ethyl acetate extracted. After drying with magnesium sulfate after rinsing and distilling off a solvent, column chromatography refines a residue, (-- 1' -- S,2' -- R,3' -- E --) - N - [-- two - (tert-butyldimethylsilyloxy)-1-[-- [-- three - (4-pyridyl methyl) -- thio -- ureido --] -- methyl --]-3-heptadecenyl --] -- PIBARU -- amide (thio ureido object) (61 mg) -- having obtained .

[0141]The thio ureido object (60 mg, 0.10mmol) acquired here was melted in the tetrahydrofuran (1.1 ml), the bottom tetrabutylammonium fluoride of ice-cooling (tetrahydrofuran 1M solution, 1.1 ml) was added, and it stirred under ice-cooling for 6 hours. Water was added to reaction mixture and ethyl acetate extracted. After drying with magnesium sulfate after rinsing and distilling off a solvent, column chromatography refines a residue, (-- 1' -- S,2' -- R,3' -- E --) - N - [-- two - hydroxy- -- one - [-- [-- three - (4-pyridyl methyl) -- thio -- ureido --] -- methyl --]-3-heptadecenyl --] -- PIBARU -- amide (35 mg) -- having obtained .

^{1}H-NMR. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.7Hz,3H),1.15(s,9H),1.20-1.43(m,22H),2.07(m,2H),3.65(m,1H),3.90(bs,1H),4.23(m,1H),4.76(bs, 2H, 5.50 (dd, J= 6.4-15.3 Hz, 1H), 5.81 (dt, J= 15.2, 6.9 Hz, 1H), 6.44 (bs, 1H), 7.26 (m, 2H), and 8.54(d, J= 5.6-Hz, 2H)MS(SIMS) m/e:533$(M+H)^+$$C_{30}H_{52}N_4O_2S$ (532) [0142]Example 803-O-(tert-butyldimethylsilyl)-2-N-isobutyryl D-erythro sphingosine (40 mg, 0.08mmol) is melted in dichloromethane (1 ml), -The bottom pyridine of 78 ** cooling (66 mg, 0.83mmol) was added, subsequently chloroformic acid trichloromethyl (26 mg, 0.13mmol) was added, and temperature up was carried out to -20 ** over 1 hour. 4-(tert-butoxycarbonylamino) aniline (87 mg, 0.42mmol) was dropped at this reaction mixture, and temperature up was carried out to the room temperature over 1 hour. After stirring reaction mixture at a room temperature for 13 hours, chloroform extracted it. The extract was rinsed after saturated sodium bicarbonate water subsequently washed, 1M chloride and. Condense after desiccation with magnesium sulfate and column chromatography refines a residue, 1-O--3-[[[4-(tert-butoxycarbonylamino) phenyl] aminocarbonyl]] O-(tert-butyldimethylsilyl)-2-N-isobutyryl D-erythro sphingosine (25 mg) was obtained.

^{1}H-NMR. ($CDCl_3$)
delta(ppm):0.00(s,3H),0.30(s,3H),0.87(t,J=6.7Hz,3H),0.90(s,9H),1.09(d,J=6.9Hz,3H),1.10(d,J=6.9Hz,3H),1.15-1.42(m, 22H),1.50(s,9H),1.92-2.09(m,2H),2.30(m,1H),4.05-4.28(m,3H),4.48(m,1H),5.42(dd,J=6.2,15.4Hz,1H),5.67(dt, J= 15.4, 6.7 Hz, 1H),5.86(d,J=7.8Hz,1H),6.46(s,1H),6.81(s,1H),7.20-7.33(m,4H) [0143]The compound (13 mg, 0.02mmol) obtained here was melted in ethyl acetate (0.7 ml), the bottom of ice-cooling 4M hydrogen chloride-ethyl acetate solution (0.3 ml) was added, and it stirred for 30 minutes under the temperature. Reaction mixture was condensed by decompression, refined the residue with thin layer chromatography, and obtained 1-O-[(4-aminophenyl) aminocarbonyl]-2-N-isobutyryl

D-erythro sphingosine (8 mg).
^{1}H-NMR. ($CDCl_3$-CD_3CD) delta. (ppm) :
0.79(t,J=6.4Hz,3H),1.01(d,J=6.8Hz,3H),1.02(d,J=6.9Hz,3H),1.00-1.40(m,22H),1.82-2.10(m,2H),2.30(m,1H), 3.92-4.30(m,4H 5.37 (dd, J= 6.3-15.4 Hz, 1H), 5.65 (dt, J= 15.4, 6.2 Hz, 1H), 6.58 (d, J= 8.4 Hz, 2H), 6.74 (bs, 1H), 7.07 (d, J= 8.4 Hz, 2H), and 8.20(s, 1H)MS(SIMS) m/e:504$(M+H)^+$$C_{29}H_{49}N_3O_4$ (503) [0144]In the chloroform (1 ml) solution of example 811-O-[[3-(dimethylamino) propyl] Aminocarbonyl]-2-N-pivaloyl D-erythro sphingosine (40 mg). Potassium bicarbonate (0.5g) was added, subsequently the methyl iodide (0.5 ml) was added, and it stirred at the room temperature for 16 hours. It condenses, after filtering a sludge, and it is 1-O-[[3-(trimethylammonio) propyl] Aminocarbonyl]-2-N-pivaloyl D-erythro sphingosine. Iodine salt (28 mg) was obtained.
^{1}H-NMR. ($CDCl_3$) delta. (ppm) : 0.88(t,J=6.6Hz,3H),1.20(s,9H),1.20-1.44(m,22H),2.02(m,2H),2.13(m,2H),3.38(s,9H),3.38(m,1H),3.56(bs,1H), 3.84(m,2H),4 . 17 (m, 2H), 4.26 (m, 1H), 4.31 (dd, J= 5.6-11.1 Hz, 1H), 5.48 (dd, J= 6.8-15.4 Hz, 1H), 5.80 (dt, J= 15.2, 6.8 Hz, 1H), 6.25 (m, 1H) and 6.36(d, J= 8.5-Hz, 1H)MS(SIMS) m/e:526(M-127)$^+$$C_{30}H_{60}IN_3O_4$ (654) [0145]Example 823-O-(tert-butyldimethylsilyl)-2-N-pivaloyl D-erythro sphingosine (0.20 g, 0.4mmol) was melted in dichloromethane (8 ml), and it cooled at -78 **. Pyridine (320microl, 4.0mmol) was added to this solution, subsequently chloroformic acid trichloromethyl (58microl-0.48mmol) was added to it, and temperature up was carried out to it to -20 ** over 1 hour. After adding the dichloromethane (5 ml) solution of 2-aminoethanol (340microl, 4.0mmol), temperature up was carried out to the room temperature over 4 hours. 1M chloride, saturated sodium bicarbonate water, water, and a saturation salt solution washed reaction mixture one by one. Distill off a solvent after desiccation with magnesium sulfate, and column chromatography refines a residue, 3-O-(tert-butyldimethylsilyl)-1-O-[(2-hydroxyethyl) aminocarbonyl]-2-N-pivaloyl D-erythro sphingosine (0.22g) was obtained.